

SAFETY ANALYSIS INSIGHT

A Comparative Analysis of Intravenous versus Oral Iron Formulations using Insights from Statistical Data

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Utilizing data mining techniques and statistical methodologies, adverse event reports from the World Health Organisation's VigiBase database were analyzed to assess the relative safety of these administration routes. The analysis revealed distinct patterns of adverse events associated with each route, with intravenous formulations showing a higher incidence of infusion-related reactions and hypersensitivity, while gastrointestinal adverse events predominated with oral supplements. Notably, hypophosphatemia emerged as a significant concern with some of the intravenous iron formulations, often overlooked in clinical practice. Furthermore, variability in safety profiles among oral formulations was observed, with implications for patient management and monitoring. These findings underscore the importance of informed decision-making in iron supplementation strategies and highlight the need for continued vigilance in recognizing and managing adverse events.

Introduction

Anaemia affects a third of the world's population, and approximately half the cases are due to iron deficiency.¹ This condition develops when there is lack of iron in the organism and is linked with decreased motor and cognitive performance and development in children, impaired physical performance and quality of life in adults, and cognitive decline in the elderly. Its aetiology is variable and there are several risk factors involved, which often coexist in an individual patient, resulting in a decrease of iron intake and absorption or an increased demand and loss.² Iron homeostasis is complex and tightly controlled.

Adaptation to iron deficiency at the tissue level is controlled by iron regulatory proteins with the aim of increasing iron uptake and retention; at systemic level, the hepatic hormone hepcidin, which mediates the process of iron homeostasis, is suppressed, leading to increased iron release to plasma by absorptive enterocytes and recycling macrophages in the spleen.^{1, 2}

The most common symptoms are nonspecific and can be attributed to lower delivery of oxygen to body tissues.² These include fatigue, shortness of breath, palpitations, pale skin and headaches.³ In addition, low iron levels also impact DNA replication and cell cycle, potentially leading to oral lesions and hair or nail abnormalities, decreased immune response, impact on neurotransmission and myelogenesis and inhibition of cytochrome P450 production, affecting drug metabolism.²

Iron deficiency anaemia is also a common comorbidity in multiple medical conditions, such as chronic kidney disease, chronic heart failure, cancer and inflammatory bowel disease, and may have detrimental effects on its clinical outcomes.^{1,2} The main groups at risk for developing iron deficiency anaemia are children aged <5 years, women in childbearing age and pregnant women.⁴

It should be noted that the diagnosis should be based on appropriate laboratory tests such as haemoglobin, serum ferritin, transferrin saturation and serum iron. Diagnosis is particularly challenging in chronic inflammatory conditions, which may mask the iron deficiency.^{1,2,4}

Besides searching for and treating the cause of iron deficiency, treatment strategies include food fortification and iron supplementation with both oral and intravenous formulations.¹ Although oral iron is usually first-line therapy, intravenous formulations are available for patients in whom oral iron is not effective or contraindicated, or when the iron deficiency is severe and there is a clinical need for a rapid iron supply. The choice between treatment with oral and intravenous iron formulations, as well as its timing, should be carefully considered as it is essential to avoid delays in iron repletion and correction of anaemia.^{1,2}

Iron is administered intravenously in the form of iron carbohydrate complexes in order to increase stability; the iron is then released from the iron-hydroxide core after absorption by macrophages and ultimately sequestered by transferrin for transport in the serum to the sites of utilisation and storage. Examples include iron sucrose, ferric carboxymaltose, sodium ferric gluconate in sucrose and various iron dextran formulations.^{5,6}

At the oral level, iron is transported into the enterocyte cytoplasm, where it can be either stored as ferritin or exported to the serum and bounded to transferrin. However, absorption of iron from the gut is carefully regulated by enterocytes and the fixed-rate physiological uptake route allows for absorption of only 5 mg at a time. Ferrous salts administered orally are also passively absorbed directly by the blood.⁵

In any case, rapid release of large amounts of iron potentially leads to transferrin saturation and circulation of non-transferrin bound iron, which is associated with oxidative stress in the tissues. Consequently, systemic adverse events including hypotension, nausea, abdominal and lower back pain, peripheral edema and a metallic taste can occur. With oral formulations, there is an additional risk of local gastrointestinal reactions induced by reactive oxygen species. In addition, iron may down regulate the expression of CD4 on the surface of T-lymphocytes, leading to immune system impairment.⁵

In general, the administration of oral formulations is easier and has a lower cost. However, the absorption is low, particularly in inflammatory conditions, and oral forms are associated with higher rates of gastrointestinal adverse events which may lead to lower adhesion to therapy. Intravenous formulations, on the other hand, although more expensive, are also more effective due to increased absorption and bioavailability, and have a negligible gastrointestinal toxicity. Nevertheless, its administration requires medically qualified personnel and appropriate facilities, and carries a risk of administration site reactions and hypersensitivity, the latest being particularly associated with dextran formulations.^{2,5}

Data Mining and Analysis of Results

Comparison of safety profiles of iron formulations administered via the afore mentioned routes was done using data from VigiBase, the World Health Organisation global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre. Data mining was performed in Empirica using Multi-item Gamma Poisson Shrinker (MGPS), which produces a statistical output called the Empirical Bayes Geometric Mean (EBGM). EBGM values provide a more stable estimate of the relative reporting rate of an event for a particular product relative to all other events and products in the database being analysed. Lower and upper 90% confidence limits for the EBGM values are denoted as EB05 and EB95, respectively.

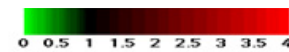
Overall safety profiles of intravenous and oral iron formulations are graphically presented by sector maps. A sector map for data mining results is a visual presentation of data for a particular drug across all MedDRA System Organ Classes (SOCs). A large tile represents each SOC in the sector map. Smaller tiles within each SOC tile represent Preferred Terms (PTs). PTs are ranked in descending order of values of EB05; high scores are shown in red and low scores in green.

Figure 1.
Sector map for intravenous iron formulations



Rank	SOC	Term (PT)	EB05
1	Genrl	Infusion site discolouration	442.554
2	Musc	Hypophosphataemic osteomalacia	242.655
3	Metab	Hypophosphataemia	177.467
4	Genrl	Infusion site extravasation	71.425
5	Genrl	Injection site phlebitis	59.714
6	Genrl	Administration site extravasation	57.951
7	Inv	Blood phosphorus decreased	55.627
8	Immun	Type III immune complex mediated reaction	53.782
9	Genrl	Infusion site thrombosis	53.322
10	SocCi	Partner stress	48.351

Figure 2.
Sector map for oral iron formulations



Rank	SOC	Term (PT)	EB05
1	Inv	Transferrin saturation increased	445.501
2	Gastr	Gastrointestinal tract mucosal pigmentation	97.703
3	Gastr	Tooth discolouration	60.265
4	Inv	Serum ferritin increased	55.881
5	Gastr	Faeces discoloured	50.957
6	Inv	Blood iron increased	50.398
7	Inv	Serum ferritin abnormal	32.779
8	Metab	Iron overload	29.705
9	Gastr	Constipation	18.215
10	Resp	Bronchostenosis	13.901

Counts of reported events were compared on SOC level and the 10 SOC's with highest number of events are presented in the table below, both for intravenous and oral formulations. As expected, the highest number of reports for intravenous forms concerned infusion/injection site reactions in General disorders and administration site conditions SOC and events from Gastrointestinal disorders SOC for oral formulations.

Table 1.

Counts of events with intravenous and oral iron formulations per MedDRA SOC

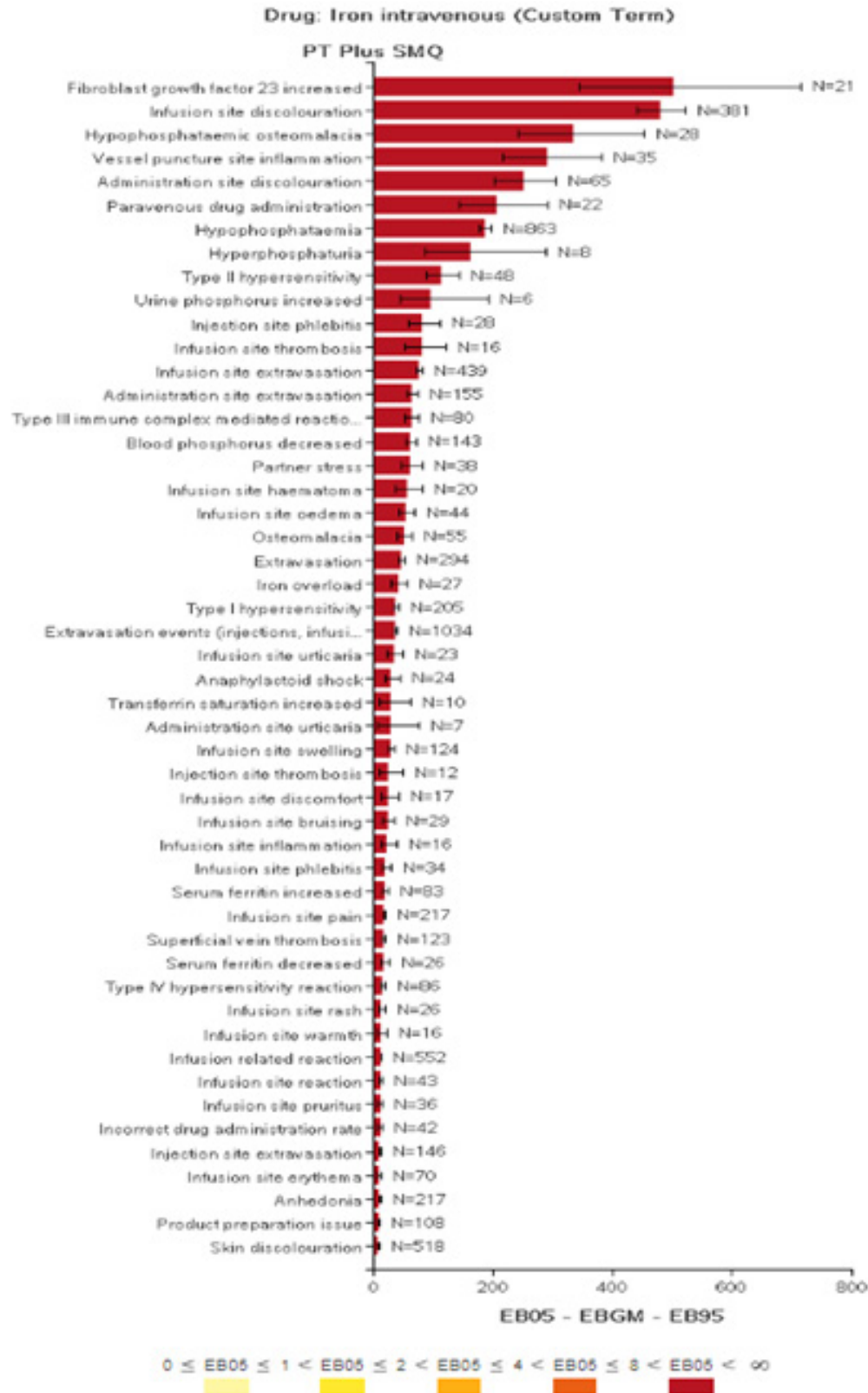
 Intravenous formulations		 Oral formulations	
MedDRA SOC	N	MedDRA SOC	N
General disorders and administration site conditions	11049	Gastrointestinal disorders	8367
Skin and subcutaneous tissue disorders	10327	Skin and subcutaneous tissue disorders	2464
Nervous system disorders	6163	General disorders and administration site conditions	1472
Gastrointestinal disorders	5723	Nervous system disorders	1248
Respiratory, thoracic, and mediastinal disorders	5446	Injury, poisoning and procedural complications	953
Vascular disorders	4680	Investigations	700
Immune system disorders	3759	Psychiatric disorders	492
Musculoskeletal and connective tissue disorders	3598	Respiratory, thoracic, and mediastinal disorders	485
Injury, poisoning and procedural complications	2370	Metabolism and nutrition disorders	421

Analysis of product-event combinations (PECs) with the highest EB05 was done for both intravenous and oral formulations.

Events with top 50 EB05 for intravenous formulations are presented in Figure 3. In line with the expectations, majority of PECs with highest scores (60%) concerned administration related issues and administration site reactions. These risks are adequately addressed in product information for iron products administered intravenously.

Fourteen percent (14%) of product-event combinations with highest EB05 concerned hypophosphatemia and related events. The product information for ferric carboxymaltose does mention that it can cause hypophosphatemia. However, this is not widely acknowledged by healthcare professionals who prescribe this iron product. Ferric carboxymaltose infusion therapy causes renal wasting of phosphate. It has been suggested that this iron compound increases serum levels of fibroblast growth factor 23 (FGF23) by inhibiting FGF23 degradation.

Figure 3.
Events with highest EB05 for intravenous iron formulations



FGF23 is a peptide secreted by both osteoclasts and osteoblasts in response to raised phosphate levels. Its function is to limit phosphate reabsorption in the renal tubules, maintaining phosphate homeostasis. Therefore, the resultant excess serum FGF23 causes hypophosphataemia by inappropriately decreasing phosphate reabsorption in the proximal renal tubules even in the presence of continued low serum phosphate levels. Additionally, FGF23 has been reported to inhibit the production of calcitriol which is needed for phosphate absorption in the intestines. Even though hypophosphatemia following iron infusion is well reported in the literature, it is under-recognized in clinical practice. In the majority of reported cases, patients were asymptomatic but, in some cases, patients experienced profound hypophosphatemia and associated symptoms. Repeated iron infusions and associated hypophosphatemia in the long term can result in osteomalacia, so it is important to monitor phosphate levels until they are maintained within the normal range and to supplement phosphate if there is severe, prolonged or symptomatic hypophosphatemia.^{7,8}

Hypersensitivity events concerned 10% of PECs with highest EB05. Hypersensitivity reactions to intravenous iron are rare but potentially life-threatening. Their management requires prompt recognition and grading of severity, together with meticulous monitoring and immediate treatment.⁹ Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation.

Overall, results of statistical analysis were in line with the known safety profile of intravenous iron formulations.

Events with top 50 EB05 for oral formulations are presented in Figure 4. Similarly to the analysis of PECs for intravenous formulations, the most frequently reported events for orally administered products are well-known; 50% of PECs with highest EB05 concerned gastrointestinal events.

Iron overload and accumulation of iron in storage sites concerned 16% of the PECs with highest EB05. There were more reports of increased serum ferritin and increased transferrin saturation in patients receiving oral formulations than with intravenous products, with EB05s also being significantly higher. Majority of cases originated from the Region of Americas. In more than 90% of reports concerning increased serum ferritin, ferrous citrate or sulfate were used; iron polymaltose was used in less than 1% of cases. The pharmacokinetics profile of iron following oral administration of iron-polymaltose complex is quite different from that of ferrous salts. The iron-polymaltose complex is made of non-ionic iron(III), in a form of polynuclear iron(III)-hydroxide, and polymaltose ligands. The resulting complex is stable. Being in a non-ionic form, iron does not interact with food components and does not induce the generation of reactive oxygen species. Pharmacokinetics of the iron(III)-polymaltose preparations have been extensively studied. During the first six hours after administration, only a negligible increase in serum iron concentration is observed, i.e., as expected from the size of the complex, there is virtually no passive diffusion through intercellular spaces. Nevertheless, 2–3 weeks after application, the incorporation of iron into erythrocytes is not significantly different to that seen with ferrous salts.¹⁰

In conclusion, statistical analysis performed for oral iron formulations also showed expected results. Other PECs with high values of EB05 did not provide new safety information that could alter their known safety profile.

Figure 4.
Events with highest EB05 for oral iron formulations



Conclusion

In this analysis, Oracle Empirica was used to build a general overview of the safety profile of intravenous and oral iron formulations using data mining techniques. It was observed that the results of this quantitative evaluation are in line with the known risks for these products. Nevertheless, the results also highlighted adverse events that, although well known, are often overlooked in clinical practice, such as hypophosphataemia and its associated clinical consequences. Interestingly, it was also possible to conclude that the safety profile of oral formulations is variable, with iron polymaltose complex showing a significantly lower risk of iron overload and accumulation in comparison with ferrous salts, which we hypothesise to be due to the increased stability of the complex.

Oracle Empirica is a powerful tool for both signal detection and analysis purposes. It allows not only to access data from large public databases, such as Vigibase, but also to translate it into statistical scores and implement diverse data visualisations in order to detect patterns and recognise trends. Besides data mining and signal analysis, PrimeVigilance also uses Empirica, through its Topics functionality, for workflow management and signal tracking, ensuring that all steps of the signal management process are adequately documented and compliant with the latest regulations.

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