Intravenous iron and osteomalacia

Introduction

Ferric carboxymaltose Ferinject® is indicated for *the treatment of iron deficiency when oral iron preparations have no effect or may not be used.* Ferric carboxymaltose Ferinject® solution for injection/infusion is a colloidal solution of the iron complex iron(III)carboxymaltose. The complex was designed as usable iron for iron transportation and storage proteins in the body (transferrine respectively ferritine). Ferric carboxymaltose Ferinject® was granted marketing authorization in the Netherlands in 2007 [1].

Iron isomaltoside 1000 Monofer® is indicated for *the treatment of iron deficiency when oral iron preparations have no effect or cannot be used, if there is a clinical necessity to administer iron fastly.* Because of the formulation of iron isomaltoside 1000 Monofer®, where the iron is present as a strongly bound complex, a controlled and delayed delivery of biological available iron takes place to the iron binding proteins with a low risk of toxicity by free iron. Iron isomaltoside 1000 Monofer® was granted marketing authorization in the Netherlands in 2009 [2].

Osteomalacia is a disorder in which at the site of bone turnover newly formed osteoid is not properly mineralized. Osteomalacia can result from an inherited genetic disease or an acquired disease. A main mechanism of osteomalacia is hypophosphatemia [3,4], typically caused by loss of phosphate in the urine. Osteomalacia can be asymptomatic or symptoms such as bone pain, muscle weakness, fractures, and impaired gait can occur [3,5,6]. There may be low bone mineral density on DXA, but presentation on DXA can be extremely variable [3]. Laboratory findings of osteomalacia depend on the underlying cause of the osteomalacia, where common findings include elevation of alkaline phosphatase, of fibroblast growth factor 23 (FGF23) and of parathyroid hormone, and a decrease of serum calcium and of phosphorous [3,5]. FGF23 is a hormone promoting phosphate excretion. FGF23 is synthesized in osteoblasts and osteocytes [3,8], and new evidence suggest also erythroid progenitor cells in the bone marrow may produce FGF23 [3,9].

Reports

Lareb database
On 5 June 2019 The Netherlands Pharmacovigilance Centre Lareb received a report of osteomalacia in association with the use of Ferinject® [10]. From 12 May 2016 to 27 August 2019 The Netherlands Pharmacovigilance Centre Lareb received two reports through the Marketing Authorisation Holder (MAH) based on reports in the scientific literature of osteomalacia in association with the use of intravenous iron, one report concerning Ferinject® and one report concerning both Ferinject® and iron sucrose Venofer®.

Report NL-LRB-00338061
This serious (disabling or incapacitating) spontaneous report from a physician concerns a female aged 30-40 years, with osteomalacia with fractures caused by excessive phosphate excretion, following administration of ferricarboxymaltose Ferinject® for Rendu-Osler-Weber syndrome with iron deficiency anaemia, with a latency of 5 years after start. Reported values of phosphate in the blood during the use of ferricarboxymaltose Ferinject® were 0.59 mmol / liter, 0.58 mmol / liter and 0.46 mmol / liter with a reference value of >0.8 mmol / liter. The drug ferricarboxymaltose Ferinject® was withdrawn. At the moment of reporting, the patient had not recovered from the reactions. Concomitant medication was omeprazole, ursodeoxycholacid, plantago ovata, calciumcarbonate/colecalciferol, colecalciferol, ethinylestradiol/levonorgestrel, sucralfate, paracetamol, codeine.

Report NL-Vifor (International) Inc.-VIT-2016-02311
Literature report: Dekker MJE DB, De Bie AJR, Kerskes CHM, Konings CJAM, Boots JJM, Krol CG; Painful bones after intravenous iron administration; 28th gathering of internal medicine specialists [11]. The aim of the study was to describe the osteomalacia and fragility fractures due to severe persistent hypophosphatemia caused by intravenous iron administration.
This case concerns a 40-50 year old male patient with a medical history of severe debilitating pain of spine and hip, gastro-intestinal arteriovenous malformations due to Rendu-Osler-Weber disease causing iron deficiency anemia, osteopenia and vertebral fractures. He had a hip replacement due to

osteonecrosis. He was concomitantly taking bisphosphates with calcium and vitamin D for osteopenia and vertebral fractures for two years.
On an unspecified date he was admitted to hospital and was treated with morphine at an unspecified high dose for an unknown indication. He was unresponsive to high dose. Lab showed hypophosphatemia (serum phosphate 0.38 mmol/L (0.80-1.50).
On an unspecified date, he had received packed red cell transfusion for iron deficiency anemia.
On an unspecified date, the patient was administered with iron carboxymaltose (Ferinject®) via intravenous route, at an unspecified dose in an unspecified dilution and given over an unspecified period of time for iron deficiency anaemia.
His hypophosphatemia was repeatedly further declining after intravenous iron supplementation and non-suppressed growth factor-23 levels 85 RU/L (<125 RU/L). His urine analysis showed renal phosphate wasting (renal phosphate excretion 25%). The patient's parathyroid hormone, vitamin D and serum calcium levels were normal. All other causes of osteopenia and fractures were excluded.
On an unspecified date, he experienced bone pain and bone fractures. On an unspecified date, he was diagnosed with hypophosphatemic osteomalacia due to intravenous iron administration. The reporter stated that on an unspecified date, the patient was hospitalized due to bone-fractures that were caused by Ferinject®. The event was treated with oral calcitriol at an unspecified dose. The patient sustained no further fractures. The therapy with Ferinject® was discontinued. The outcome of events hypophosphatemic osteomalacia and bone fractures was unknown. On an unspecified date in 2016, the patient had recovered from the events hypophosphatemia declined and bone pain.

Report NL-Vifor (International) Inc.-VIT-2018-04903.
This initial spontaneous case was received on 15 May 2018 from a physician in the Netherlands via a literature report: Brouwers K, Hoorn E, Siersema P. Hypophosphataemia is a risk of intravenous iron products [Hypofosfatemie is risico bij intraveneus ijzerpreparaat] Pharmaceutisch Weekblad 18,04-05-2018 [12].

Other sources of information

SmPC

The Dutch SmPC of ferric carboxymaltose Ferinject® does mention hypophosphatemia as a common (1-10%) adverse drug reaction. The Dutch SmPC of ferric carboxymaltose Ferinject® does not mention osteomalacia as adverse drug reaction [1].
The Dutch SmPC of iron isomaltoside 1000 Monofer® does mention hypophosphatemia as an uncommon (0.1-1%) adverse drug reaction. The Dutch SmPC of iron isomaltoside 1000 Monofer® does not mention osteomalacia as adverse drug reaction [2].

The FDA label of ferric carboxymaltose Injectafer® reports as postmarketing experience: “One case of hypophosphatemic osteomalacia was reported in a subject who received 500 mg of Injectafer® every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectafer®.” [13].

Literature

In the scientific literature several cases were described concerning osteomalacia in association with treatment with intravenous iron, including the following cases.
A 57-year-old man with Crohn's disease and chronic iron-deficiency anaemia receiving multiple doses of ferric carboxymaltose developed severe hypophosphatemic osteomalacia with urinary phosphate loss and increased FGF23. Only months after ferric carboxymaltose discontinuation and aggressive phosphate repletion FGF23 excess and osteomalacia resolved [14].
A 42-year-old man with Crohn's disease presented with persistent hypophosphatemia and insufficiency fractures while receiving regular iron infusions due to chronic gastrointestinal bleeding. Monthly intravenous iron therapy with highdose ferric carboxymaltose (1000 mg, monthly), was started about 1.5 years before. Retrospectively, serum phosphate concentration had been low over the last 1.5 years, at about the same time when intravenous iron therapy with ferric carboxymaltose was started. The 24-hour urine phosphate excretion indicated renal phosphate wasting [15].
A 77-year-old female experienced hypophosphatemic osteomalacia and finally resulting in an insufficiency fracture of medial proximal tibia after 2-year administration of 80 mg/week of intravenous saccharated ferric oxide for iron deficit anemia due to duodenum ulcer. By withdrawing saccharated ferric oxide administration and rest, the hypophosphatemia and pain due to the insufficiency fracture

were recovered promptly. The patient also had a varus deformity of the knee associated with osteoarthritis, which may also have caused the insufficiency fracture of the medial proximal tibia in addition to osteomalacia [16].
A review article titled “Iron-induced hypophosphatemia: an emerging complication” of Zoller *et al* published in 2017, describes 15 cases reported in the scientific literature of iron-induced hypophosphatemia with osteomalacia as associated complication. The involved iron preparations concerned saccharated iron oxide in 10 cases, iron polymaltose in 1 case, ferric carboxymaltose in 3 cases, and both iron sucrose and ferric carboxymaltose in 1 case [17].
Recently an article was published in the *Nederlands Tijdschrift voor Geneeskunde*, concerning iron supplementation in iron deficiency anaemia, in which hypophosphatemia in association with parenteral iron, osteomalacia in association with long-term existing hypophosphatemia and advises concerning measurements of phosphate concentrations when administering parenteral iron, were described [18].

Databases

Table 1. Reports of the PT Osteomalacia and the PT Hypophosphataemic osteomalacia associated with the use of iron preparations in the Lareb database, Eudravigilance and the WHO database [10,19,20].

Database	Drug	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	ferricarboxymaltose Ferinject®	Osteomalacia	3	240.8 (63.7 - 911.2)
	iron sucrose Venofer®	Osteomalacia	1	
Eudravigilance	ferriccarboxylmaltose	Osteomalacia	24	41.5 (27.6 – 62.4)
	ferriccarboxylmaltose	Hypophosphataemic osteomalacia	6	195.8 (82.7 – 463.4)
	ferric hydroxide polymaltose complex	Osteomalacia	1	
	iron sucrose	Osteomalacia	3	13.3 (4.3 – 41.5)
	iron sucrose	Hypophosphataemic osteomalacia	1	
	ironIII isomaltoside 1000	Osteomalacia	1	
WHO	ATC5 B03A Iron preparations	Osteomalacia	36	21.8 (15.7-30.6)
	ATC5 B03A Iron preparations	Hypophosphataemic osteomalacia	6	162.8 (64.6-410.1)

Prescription data

The number of patients using ferricarboxymaltose Ferinject® or iron sucrose Venofer® in the Netherlands cannot be indicated by use of the GIP database (the database in the Netherlands providing information on drug use based on data of the health insurance companies), because ferricarboxymaltose Ferinject® or iron sucrose Venofer® are administered in the hospital and provided by hospital pharmacies [21].

Mechanism

Especially sugar bound intravenous iron preparations can cause a rise in FGF23 levels, resulting in hypophosphatemia [22]. It has been suggested that the carbohydrate moiety of iron preparations interferes with the proteolytic degradation of FGF23, based on a rapid reduction in the c-terminal portion of FGF23 and, conversely, an increase in intact FGF23 in women receiving intravenous iron for dysfunctional uterine bleeding [23,24]. A previous study suggested that after approximately 1–2 weeks following iron polymaltose infusion the nadir in serum phosphate levels occurs, coinciding with a significant rise in FGF23 concentrations, maximal renal phosphate loss and a significant reduction in 1,25-dihydroxy vitamin D levels [23,25]. It was determined in another study that the biochemical abnormalities following administration of ferric carboxymaltose may persist for up to 6–12 weeks [23,26], supporting regular clinical review of at-risk patients [23]. Severe hypophosphataemia can result in osteomalacia [22,27].

Discussion and conclusion

Netherlands Pharmacovigilance Centre Lareb received one spontaneous report of osteomalacia in association with the use of Ferinject® and two reports through the MAH based on reports in the scientific literature of osteomalacia in association with the use of intravenous iron, one report concerning Ferinject®, and one report concerning both Ferinject® and iron sucrose Venofer®. In the scientific literature several cases were described concerning osteomalacia in association with treatment with intravenous iron.
Mechanistically, especially sugar bound intravenous iron preparations can cause a rise in FGF23 levels [22], resulting in hypophosphatemia as FGF23 is a hormone promoting phosphate excretion, [3,8], where severe hypophosphatemia can result in osteomalacia [22,27].

Based on the reports including reports from the scientific literature described in this signal, it is suggested that treatment with intravenous iron can through hypophosphatemia result in osteomalacia.
Currently, the SmPC's of ferric carboxymaltose Ferinject® and iron isomaltoside 1000 Monofer® do mention hypophosphatemia as an adverse drug reaction, but do not contain advices on measurements of blood phosphate values, and do not mention osteomalacia as an adverse drug reaction.

References

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2. Dutch SmPC ijzer(III)isomaltoside-1000 Monofer® 100 mg/ml oplossing voor injectie/infusie. (version date: 22-5-2019, access date: 19-9-2019) https://www.geneesmiddeleninformatiebank.nl/smpc/h103070_smpc.pdf;
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17-01-2020: Addition to the Signal "Intravenous iron and osteomalacia" 27/11/2019.

In table 1 of this Signal one report in the Eudravigilance database of the reaction osteomalacia in association with ironIII isomaltoside 1000 was reported. After publishing this Signal it was reported that in this report in the Eudravigilance database ferriccarboxylmaltose was the drug associated with the reaction osteomalacia and not ironIII isomaltoside 1000.

This signal has been raised on November 27, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl