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Hypophosphatemia after treatment with parenteral iron: case report

Hipofosfatemija po zdravljenju s parenteralnim železom: prikaz primera

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Abstract

Iron deficiency anaemia is the most common anaemia worldwide, affecting mainly children, women of childbearing potential and pregnant women, and is increasingly present in chronic patients and the elderly population. The basic method of replacement is oral preparations, which often cause side effects, but sometimes this type of replacement is insufficient, due to lack of intake, i.e., gastrointestinal malabsorption or persistent bleeding. Another way is the parenteral replacement, in recent years most commonly with ferric carboxymaltose. This medicine is safe, and its side effects are relatively rare and mostly mild to moderate. Of the metabolic disorders, the most common is hypophosphatemia, the incidence of which has not yet been clearly defined in the literature but is not negligible. In most cases, it is asymptomatic and transient, but can also be severe and long-lasting. The paper describes the case of a young patient with severe symptomatic hypophosphatemia of 0.24 mmol/L after ferric carboxymaltose applications. We add a brief review of the literature and an algorithm of clinical action.

Izvleček

Anemija zaradi pomanjkanja železa je najpogostejša anemija na svetu, ki prizadene predvsem otroke, ženske v rodni dobi ter nosečnice, vse pogosteje pa spremlja tudi kronične bolnike in populacijo starejših ljudi. Osnovni način nadomeščanja so peroralni pripravki, ki nemalokrat povzročijo neželene učinke. Včasih tovrstno nadomeščanje ne zadošča zaradi pomanjkljivega privzema oziroma absorpcije v prebavilih ali zaradi stalnih krvavitev. Drugi način je parenteralno nadomeščanje, ki se v zadnjih letih najpogosteje izvaja z železovo karboksimaltozo. Zdravilo je varno, neželeni učinki pa so razmeroma redki in povečini blagi do zmerni. Od presnovnih motenj je najpogostejša hipofosfatemija, katere incidenca glede na literaturo še ni povsem jasno opredeljena, a ni zanemarljiva. V večini primerov sicer poteka brez simptomov in je prehodna, lahko pa je tudi huda in dolgotrajna. V prispevku opisujemo primer mlade bolnice s hudo hipofosfatemijo 0,24 mmol/L s simptomi po aplikacijah železove karboksimaltoze. Dodajamo kratek pregled literature in algoritem kliničnega ukrepanja.

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1 Introduction

Iron deficiency anaemia is the most common type of anaemia worldwide (1). It is a major contributor to the overall burden of disease on society. It mostly affects children, women of childbearing potential and pregnant women, and is increasingly present in patients with chronic conditions and the elderly population (2). It is estimated that hundreds of millions of people worldwide are affected (1). The causes of iron deficiency are numerous and can occur from a combination of factors. These range from insufficient or inadequate nutrition, reduced iron intake in the gastrointestinal tract or blood loss (1). Malnutrition is the major cause in the underdeveloped world, whereas blood loss accounts for the condition in the developed world, loss due to bleeding (3). Given that iron deficiency anaemia is usually due to another medical condition, the main cause needs to be clarified; early detection of the possibility of underlying cancer is of paramount importance (3).

Iron is replaced in two ways, by oral preparations and parenterally. The basic method of replacement is oral preparation, which can often cause side effects, affecting digestion in particular. At times this type of replacement is ineffective due to a lack of absorption in the gastrointestinal tract, or due to constant bleeding. It can also exacerbate chronic inflammatory bowel disease (3). Two parenteral replacement drugs have been on the market in Slovenia for several years now: ferric oxide saccharate and ferric carboxymaltose (3). In recent years, the latter has been increasingly used as it is considered safe with relatively rare side effects, confirmed by numerous studies and meta-analyses (4,5). One U.S. comparative study was carried out that involved 352 patients with postpartum sideropenic anaemia; 174 patients received ferric carboxymaltose and 178 patients received oral iron sulphate. In the former group, injection were ceased in only one patient due to skin rashes (6).

Reactions to ferric carboxymaltose treatment are mostly mild to moderate (7). The most commonly reported are: nausea; dizziness; skin rash in the form of urticaria; reaction at the site of intravenous administration. Patients can also experience abdominal pain, although very rarely, as well as constipation and diarrhoea (7,8). After ferric carboxymaltose application, the most common metabolic disorder to occur is hypophosphatemia, the incidence of this is not yet clearly defined in the literature, but can not be considered negligible (9,10). In most cases, it is asymptomatic and transient, but it can also be severe and long-lasting (10). This article describes the case of a young patient, who developed severe hypophosphatemia with symptoms after ferric carboxymaltose application.

2 Case presentation

A 33-year-old patient with known psoriasis undergoing biological treatment was referred to a haematology clinic due to moderate iron deficiency anaemia. Until recently, the anaemia had been treated by a personal physician with oral iron replacement. Her latest check-up showed a low blood count despite regularly taking oral iron supplements. As a result of the ineffectiveness of the previous treatment for psoriasis, in the following 6 months the patient started to receive the biological drug infliximab, and her disease came under control. The patient herself suggested that there may be a link between the initiation of the biological therapy and the ineffectiveness of oral iron replacement, as she found it increasingly difficult to tolerate oral therapy, and painful abdominal cramps had become more common.

During a check-up at the Department of Haematology, she complained of fatigue, weakness, frequent headaches, a decrease in physical performance, and shortness of breath on exertion, but claimed not to have palpitations, dizziness, chest pain or dyspnoea. She also denied infection, including fever and chills, heartburn, B-symptoms (i.e. weight loss, fever and night sweats), nausea, vomiting, diarrhoea, nor any signs of bleeding, including in stools and urine. Menstruation was normal, with no heavy bleeding or bleeding between periods, and no abnormalities were observed during the gynaecological examination. Her personal doctor referred her for gastrointestinal endoscopy. Esophagogastroduodenoscopy (EDGS) as well as colonoscopy did not reveal any pathology. A test for *Helicobacter pylori* was negative. A duodenal biopsy did not reveal possible celiac disease. She ate a variety of foods, including meat products, claimed not to be on any diet, nor did she experience any changes in digestion after eating a certain type of food, such as cereals. She did not mention any cancer cases in the family, although her mother was treated with radioactive iodine for hyperthyroidism. Aside from pale skin and mucous membranes which showed no signs of bleeding during the clinical examination, there were no significant deviations, such as possible peripheral lymph

nodes nor enlarged liver or spleen to the touch.

The complete blood picture showed moderate levels of microcytic hypochromic anaemia with haemoglobin 98 g/L, haematocrit 0.30, mean corpuscular volume (MCV) 78.9 fL, mean corpuscular haemoglobin (MCH) 25.8 pg. Platelet and leukocyte levels were within normal limits (304 x 10^9/L and 7.76 x 10^9/L, respectively). The differential blood count was within normal limits. The biochemical results showed laboratory indicators of depleted iron stores with a greatly reduced ferritin of 8 µg/L and a transferrin saturation of 7.3%. Other results were without significant deviations, with special emphasis on the fact that phosphate and calcium levels were within normal limits and renal function was also without deviation, as shown in Table 1. A closer examination by analysis of previous laboratory tests showed that biochemical results, including phosphate, calcium and renal function, have been stable in the past.

According to anamnestic data, clinical examination, and laboratory tests, anaemia was present due to iron deficiency. We predicted poorer absorption of iron in the gastrointestinal tract as possible cause. Due to the failure and intolerance of oral iron preparations, we decided to parenterally replace iron with ferric carboxymaltose at a dose of 500 mg once a week for three consecutive weeks. The medicine was diluted in 100 ml of saline according to the manufacturer's instructions, and the infusion ran for approximately thirty minutes (15 minutes would

Table 1: Biochemical laboratory findings of the patient before the first application of ferric carboxymaltose, during the onset of symptoms and when hypophosphatemia disappears.

Laboratory parameter and reference values	During first application	A week after the first application	Three months after the first application
Ferritin (20-300 µg/L)	8 µg/L	/	121 µg/L
Iron (10.7-28.6 µmol/L)	4.8 µmol/L	/	20.4 µmol/L
TIBC (44.8-80.6 µmol/L)	66.2 µmol/L	/	47.9 µmol/L
Transferrin saturation (15-45%)	7.3%	/	42.6%
Sodium (135-145 mmol/L)	141 mmol/L	141 mmol/L	139 mmol/L
Potassium (3.8-5.5 mmol/L)	3.9 mmol/L	4.0 mmol/L	3.8 mmol/L
Chloride (95-105 mmol/L)	106 mmol/L	110 mmol/L	106 mmol/L
Calcium (2.1-2.6 mmol/L)	2.25 mmol/L	2.08 mmol/L	2.28 mmol/L
Phosphate (0.84-1.45 mmol/L)	**1.35 mmol/L**	**0.32 mmol/L**	**0.75 mmol/L**
Creatinine (44-97 µmol/L)	61 µmol/L	53 µmol/L	61 µmol/L
Urea (2.8-7.5 mmol/L)	3.3 mmol/L	3.5 mmol/L	3.8 mmol/L
GFR	above 90 ml/min	above 90 ml/min	above 90 ml/min
Glucose (3.6-6.1 mmol/L)	4.6 mmol/L	4.8 mmol/L	3.6-6.1 mmol/L
Urate (150-480 µmol/L)	222 µmol/L	243 µmol/L	223 µmol/L
AST (up to 0.52 µkat/L)	0.64 µkat/L	0.42 µkat/L	0.41 µkat/L
ALT (up to 0.57 µkat/L)	0.45 µkat/L	0.30 µkat/L	0.30 µkat/L
g-GT (up to 0.63 µkat/L)	0.39 µkat/L	0.30 µkat/L	0.42 µkat/L
AF (0.55-1.64 µkat/L)	0.74 µkat/L	0.63 µkat/L	0.81 µkat/L
Bilirubin (tot.) (3-22 µmol/L)	9 µmol/L	8 µmol/L	13 µmol/L
Bilirubin (dir.) (up to 7 µmol/L)	2 µmol/L	2 µmol/L	3 µmol/L
Albumin (32-55 g/L)	43 g/L	/	48 g/L
LDH (up to 4.12 µkat/L)	3.17 µkat/L	4.39 µkat/L	3.11 µkat/L

have been enough). During and immediately after the drug application, the patient reported no problems, but within a few hours after each application of the drug, she experienced painful cramps throughout the abdomen, but there were no changes in the discharge of water and feces. She also stated she did not have heartburn, pain elsewhere in the body, no appearance of skin rash or swelling, dyspnoea, palpitations, dizziness, loss of consciousness, nor any neurological symptoms, including disorders of consciousness, cognitive impairment, convulsions, muscle weakness, paraesthesias and swallowing disorders.

The patient was clinically examined prior to the third application of the drug, and no significant deviations were recorded. The decision was made to control the biochemical results. After subsequent receipt of all results, it was obvious that severe hypophosphatemia had occurred this time with a phosphate level of 0.32 mmol/L. Levels of other electrolytes were stable, and renal and hepatic function did not deteriorate. After consultation with a consultative endocrinologist, we introduced oral replacement with one gram or one powder preparation of phosphate powder three times a day (approx. 20.1 mmol phosphate per day; 1 gram or powder contains 6.7 mmol of phosphate) and simultaneous replacement of magnesium with magnesium citrate 150 mg daily. The level of magnesium was at the lower limit, i.e., 0.71 mmol/L (RR: 0.6-1.1 mmol/L): phosphate in the gastrointestinal tract forms a bond with magnesium, which makes it more difficult to absorb.

After two days, the hypophosphatemia worsened despite taking phosphate powders. The phosphate level was 0.24 mmol/L. Whilst the patient experienced no other new problems, she reported escalating drowsiness, which was more pronounced than before the first infusion of ferric carboxymaltose. Additional parenteral potassium phosphate (K_3PO_4) replacements were chosen. She received an infusion of 40 mmol preparation in 250 ml of saline, increasing the oral dose to two grams three times a day. The next day, the level dropped slightly to 0.24 mmol/L, so we repeated the same parenteral dose (40 mmol) and then again for the third day; control before the third application already showed an increase in phosphate to 0.42 mmol/L. On the fourth day, the phosphate level increased to 0.61 mmol/L, therefore parenteral treatment was discontinued and the oral dose was reduced to one gram twice daily. The drowsiness gradually disappeared and the patient did not report any other new problems. The blood count showed an increase in haemoglobin, which we expected, given the iron therapy beforehand.

3 Discussion

Hypophosphatemia is a condition that occurs when blood phosphate levels are below 0.8 mmol/L (11). It can create a diverse clinical picture, depending on the duration of the deficiency and concentration of phosphate; most patients have no symptoms. The development of the problems described below occurs when the phosphate level falls below 0.32 mmol/L (11). Symptoms are due to a decrease in adenosine triphosphate (ATP) stores, causing ATP-dependent cellular functions to fail. In addition, the levels of 2,3-diphosphoglycerate in erythrocytes are lowered, which increases the affinity of haemoglobin for oxygen, thereby reducing the release of oxygen from haemoglobin at the periphery, i.e. at the tissue level (12). In the central nervous system, the consequences are manifested by a variety of symptoms ranging from mild paraesthesias and irritability to severe disorders with the development of delirium, generalized convulsions, and disorders of consciousness, including coma (12,13). Phosphate deficiency may impair myocardial contractility and is also associated with a higher incidence of ventricular arrhythmias with the development of acute myocardial infarction (12,13). Weakness of the diaphragm can impede breathing and also contribute to a more difficult respirator withdrawal of patients in intensive care units (12,13). The proximal skeletal muscles are also weakened, swallowing disorders can occur, and ileus may develop due to the effect on smooth muscles (12,13). Acute lowering of phosphate levels in the presence of pre-existing hypophosphatemia may even lead to rhabdomyolysis, with the actual hypophosphatemia being obscured by the release of phosphate from disintegrated cells (12,13). Effects on blood cells are rare and only occur in severe hypophosphatemia. Effects include haemolysis due to increased erythrocyte rigidity and impaired leukocyte and platelet function (12,13). Due to bone resorption, chronic severe hypophosphatemia can lead to osteomalacia and consequently to bone pain and fractures (12).

The clinical picture in the initial weeks after the first infusion was not typical in our patient. The illness manifested itself only by painful abdominal cramps that lasted one to two days after application, which could fall within the scope of hypophosphatemia. However, we have allowed for the possibility that it was a stand-alone side effect of the drug. At the onset of severe hypophosphatemia, she reported somnolence, which could be described as a mild disorder of consciousness in the context of neurological symptoms; no possible development of other symptoms was recorded. With the improvement

of the anaemia and the replenishment of iron stores, the escalation of somnolence and the new appearance of painful cramps cannot be attributed to anaemia due to iron deficiency.

Hypophosphatemia may occur with phosphate transfer to cells (e.g. refeeding syndrome in previously starving patients due to hormonal and metabolic changes, respiratory alkalosis, and treatment of diabetic ketoacidosis), with renal phosphate loss (e.g. primary hyperparathyroidism, congenital and acquired impairment of the proximal tubules in the kidneys) and with reduced gastrointestinal absorption of phosphates (e.g. alcoholism, chronic diarrhoea and taking large amounts of antacids) (13). It is important to mention here the fibroblast growth factor 23 (FGF23), which is secreted from osteoblasts in bone and is important for phosphate homeostasis as it reduces reabsorption and increases phosphate excretion. Elevated levels of FGF23 are found in chronic renal failure, but may be present as paraneoplastic in some tumour diseases, for example, which may then lead to the development of tumour osteomalacia (14,15). Studies have shown that ferric carboxymaltose can cause an increase in FGF23 levels and thus hypophosphatemia due to renal phosphate loss, which may persist for several months after the last infusion of the drug (16). The effect of phosphate deficiency and loss through the kidneys may show up after just a few days (17).

The incidence of hypophosphatemia after treatment with parenteral iron is not completely clear. Several studies have shown that mild to moderate asymptomatic hypophosphatemia occurs spontaneously after infusions of ferric carboxymaltose and resolves spontaneously within a few weeks (10). The incidence varies considerably between studies; the range is from 3% to more than 80%. Thus, Evstatiev et al., for example, noted in a study of 485 patients, half of whom received ferric carboxymaltose and half received ferric saccharate, an incidence of hypophosphatemia of 2.5% in the carboxymaltose group, with phosphate levels falling from a basal value of 1.12 ± 0.22 per 0.69 ± 0.24 mmol/L two weeks after application and then spontaneously returning to normal between four and twelve weeks after the application of carboxymaltose. No symptoms were reported in patients. No hypophosphatemia was reported in the other group (18). Some other studies describe higher incidences than those listed in Table 2 (19-22). Retrospective studies comparing ferric carboxymaltose with other parenteral preparations or with placebo have been reported. In some cases, the duration of hypophosphatemia is not adequately defined, as patients received multiple consecutive iron infusions.

It should be noted that the patient had been treated for psoriasis with the monoclonal antibody infliximab until she started to receive ferric carboxymaltose. She had been receiving the medicine regularly for more than half a year. Phosphate levels were within normal limits. When taking infliximab, she did not have the previously described symptoms, so we believe that this medicine was less likely to be the cause of hypophosphatemia. We have not found descriptions in the literature that would link infliximab to hypophosphatemia.

In the treatment of hypophosphatemia, treating the cause that led to the disorder described is essential. A brief overview of the substitution treatment is shown in Table 3. In the case of our patient, the first phosphate level measured was verging on being severe but with no typical symptoms. Therefore, we initially opted for oral replacement. Over the next two weeks, a combination of oral and parenteral replacement was required due to persistence of severe hypophosphatemia, which

Table 2: Incidences of hypophosphatemia following parenteral iron application in various retrospective studies.

Study	Parenteral iron	Incidence of hypophosphatemia	Duration of hypophosphatemia	Development of severe hypophosphatemia (<0.32 mmol/L)
Hardy, Vandemergel; 2015 (19)	ferric carboxymaltose vs. iron sucrose	51% vs. 22%	6 months on average (range 2-9 months)	13 % vs. 0%
Favrat et al.; 2014 (PREFER) (20)	ferric carboxymaltose vs. placebo	86% vs. 2%	up to 8 weeks	no
Barish et al.; 2012 (21)	ferric carboxymaltose vs. alternative replacement	7% vs. 0%	up to 6 weeks	no
Bager et al.; 2016 (22)	ferric carboxymaltose vs. iron isomaltoside	50% vs. <10%	at least 10 weeks	11% vs. 0%

Table 3: Biochemical laboratory findings of the patient before the first application of ferric carboxymaltose, during the onset of symptoms and when hypophosphatemia disappears. Summarized after Gubenšek, J, 2018 (13).

Degree of hypophosphatemia	Serum phosphate concentration	Oral replacement	Intravenous replacement
*Mild	0.65-0.32 mmol/L	phosphate powders 1-2 g 3 to 4 times a day; phosphate-rich food intake	in case of poor intestinal absorption potassium phosphate or potassium glycerophosphate 0.08-0.24 mmol/kg
**Severe	under 0.32 mmol/L	with an increase above 0.48 mmol/L, intravenous replacement is discontinued and switched to oral	potassium phosphate or potassium glycerophosphate 0.25-0.5 mmol/kg 8-12 hours

*Mild hypophosphatemia is treated with oral replacement. ** In severe hypophosphatemia, the treatment is switched to parenteral replacement, while paying attention to an increase in phosphates.

gradually resolved. We also controlled vitamin D3 levels, as deficiency can lead to hypophosphatemia. This was 49 nmol/L which indicated a moderately good vitamin D supply (23). The problems with cramps and somnolence completely disappeared with phosphate replacement. Three months after the first administration of ferric carboxymaltose, phosphate levels practically returned to normal, above 0.75 mmol/L, and other laboratory results were within normal limits, as shown in Table 1.

4 Conclusion

Parenteral iron replacement quickly, effectively, and safely corrects iron deficiency anaemia. It is used in cases of intolerance or ineffective oral iron replacement. In Slovenia, ferric carboxymaltose is currently the most commonly used.

Studies show that a certain proportion of patients develop hypophosphatemia, usually mild to moderate, without symptoms, which resolves spontaneously within a few weeks after treatment with parenteral iron. Severe hypophosphatemias with symptoms are relatively rare. In cases of a characteristic clinical picture with muscle weakness, neurological symptoms, impaired consciousness and/or difficulty breathing, which may appear as early as a few days after the infusion, phosphate levels should be monitored and appropriate action taken. A simple action algorithm is summarized in

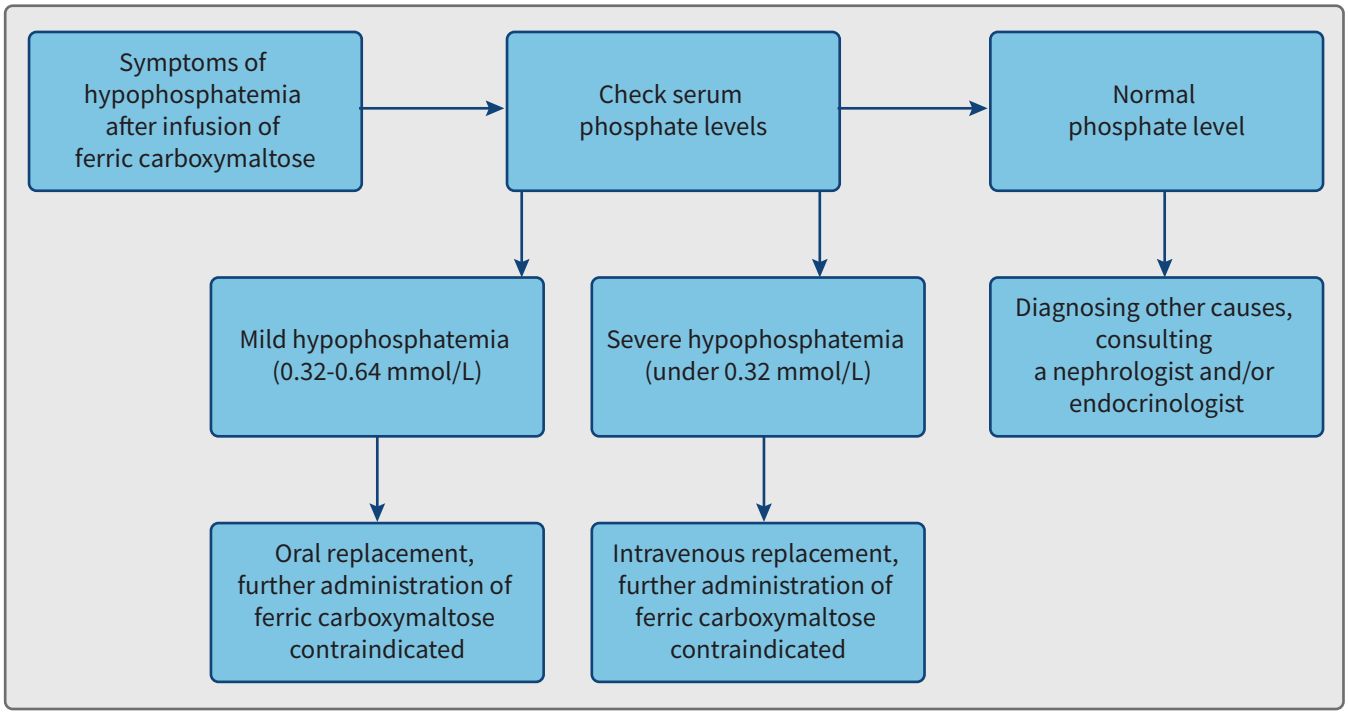

Figure 1: Algorithm of action in case of clinical symptoms of hypophosphatemia after infusion of ferric carboxymaltose.

Figure 1. Further applications of ferric carboxymaltose are, of course, out of place. Due to all the stated facts, we emphasize that it makes sense to monitor the level of phosphate before the first application of ferric carboxymaltose and in any event after it with symptoms characteristic of hypophosphatemia.

Conflict of interest

None declared.

Inform consent of the patient

The patient gave informed consent for the publication of her case.

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