

Administration of iron-containing drugs in non-dialyzed patients with chronic kidney disease

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Abstract: In the review paper an issue of the administration of iron containing drugs in the treatment of anemia in non-dialyzed patients with chronic kidney disease (CKD) is presented. Iron deficiency in patients with CKD (serum ferritin concentration below 100 ng/ml, transferrin saturation below 20%) occurs in 20–70% of cases. Prevalence of iron deficiency depends on stage of CKD and patients' gender. Among causes of iron deficiency the following reasons are mentioned: blood loss through gastrointestinal tract (17–18% of patients in pre-dialysis stage show positive results of tests on occult blood), diminished absorption (uremic gastroenteropathy, administration of drugs decreasing iron absorption), decreased delivery of food (anorexia, low protein diet), infections and inflammatory state. In the course of infections and inflammatory states body iron storage may be normal, but its utilization for erythropoiesis is deteriorated (functional iron deficiency). Results of randomized controlled studies indicate greater efficiency of intravenous therapy in comparison with oral route of iron administration. In practice, the main route of administration of iron – containing drugs to non-dialyzed patients with CKD remains, however, the oral one (iron sulfate, iron fumarate, hem iron) as more convenient and seldom leading to serious side effects. Intravenous iron therapy (iron dextrose, iron polymaltose, sodium-iron gluconate, iron sucrose) is required for cases with absolute deficiency of this microelement, disturbed intestinal absorption, poor tolerance of oral iron medication or its ineffectiveness from other reasons. Administration of erythropoiesis stimulating agents in predialysis period may require intravenous iron therapy because of enhanced consumption of its stores for erythropoiesis. Attention should be paid to possible nephrotoxic effects of administration of iron containing drugs (transient proteinuria, damage of renal tubules, decrease in glomerular filtration rate).

Key words: anemia, chronic kidney disease, iron, side effects

Incidence of iron deficiency

The treatment with iron is one of the elements of anemia treatment in patients with chronic kidney disease (CKD) [1,2]. The American authors observed a statistically significant decrease of the hemoglobin (Hb) level in males with 60–70 ml/min and females with 40–50 ml/min Cockcroft-Gault equation estimated creatinine clearance [3,4]. In the USA in 2002 the CKD associated anemia (Hb <11 g/dl) was diagnosed in 80 000 adult patients [4]. European trials showed that no more than 32% of the pre-dialyzed CRF patients achieve Hb >11 g/dl [5]. In Romania 89% of patients beginning renal substitution therapy do not reach 10 g/dl of the hemoglobin level [6].

The European Best Practice Guidelines (EBPG) [1] as well as American [2] guidelines recommend the use of iron serum level, transferrin saturation (TSAT) and reticulocyte hemoglobin content (CHr) as iron metabolism parameters [1,2]. According to the EBPG a percentage of hypochromic erythrocytes is the most appropriate marker of functional iron deficiency [1]. If there is no possibility of performing the test the patient should be referred to the clinic where the test is

available and where the erythropoietin stimulation therapy is possible to perform according to the National Health Fund requirements.

In the CRF patients with a stable Hb level without erythropoiesis stimulating agents (ESA), iron body resources should be evaluated every 2–6 months [1]. During treatment with the ESA the iron parameters should be evaluated every month initially and at least every three months after the optimal maintaining the ESA dose is established [2].

In the case of absolute iron deficiency (serum ferritin <20 ng/ml) iron reserves are too scant to detect them with staining [7]. In the CKD patients absolute iron deficiency is impossible to define. In non-dialyzed patients serum ferritin below 25 ng/ml in men and 12 ng/ml in women suggests iron deficiency to

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be the reason of anemia [2]. In dialyzed patients ferritin serum 100 ng/ml is the lower limit of normal (LLN) of iron reserve [1], because no iron reserve was observed with serum ferritin up to 200 ng/ml and higher [8]. Research indicates that serum ferritin decreased to below 100 ng/ml is a determinant of iron deficiency [9,10] because iron treatment efficacy is not only limited to iron-deficient patients [2].

Iron deficiency in patients beginning renal substitution is diagnosed when serum ferritin decreases to below 100 ng/ml. It occurs in 39% of cases [9]. The analysis performed in two university clinics showed iron deficiency in 54% of predialyzed patients [10]. Hsu et al. [11] demonstrated iron deficiency (TSAT <20%, serum ferritin <100ng/ml) in 20–70% of non-dialyzed patients with CKD. The incidence of iron deficiency depended on the CKD stage and gender.

Etiology of iron deficiency

There are several papers concerning etiology of iron deficiency in pre-dialyzed patients [12,13]. One of them is the gastrointestinal blood loss confirmed by a positive fecal occult blood test in 17–18% of pre-dialyzed patients [14,15]. The fecal blood loss was estimated to be 3.15 ml/24h what is an intermediate value between healthy volunteers (0.82 ml/24h) and dialyzed patients (6.27 ml/d) [16]. Uremic gastroenteropathy and coagulation disorders are the reasons for blood loss often caused by platelet dysfunction. It is also caused by the chronic administration of acetylsalicylic acid because of cardiologic reasons [17].

Furthermore, iron deficiency results from a decreased uptake caused by anorexia and a low-protein diet. It is intensified by frequent infections and inflammatory processes, and the urine iron loss while proteinuria even up to 1 mg/24h [18]. Iron malabsorption existing before the CKD diagnosis as well as appearing or intensifying as a result of uremic toxemia is significant. Iron absorption reducing drugs (calcium carbonate, sodium hydroxide, H_2 -proton pump inhibitors) can lead to iron deficiency even if the uptake is adequate [19,20].

Before starting iron supplementation it is necessary to diagnose the etiology and – if possible – eliminate the cause of iron deficiency. The diagnostic tests such as blood coagulation test, oral iron absorption test, diet analysis, inflammatory process markers, medication analysis and proteinuria evaluation should be performed. The diagnostic value of the fecal occult blood test is low because it is often false negative in colorectal cancer and precancerous polyps of the colon [2].

Iron administration route

In the non-dialyzed CKF patients iron is usually administered orally. Intravenous therapy is inevitable in the case of absolute iron deficiency, enteric malabsorption, oral iron intolerance, or ineffectiveness for other reasons (e.g. irregular intake).

These indications are of practical reasons because iron intravenous administration results in a better outcome. Accord-

ing to the EBPG oral administration can be considered in non-dialyzed patients [1]. American guidelines allow both intravenous and oral iron administration in non-dialyzed patients [2].

The ferrous sulphate is an iron preparation widely used in Poland. The other one – with a good iron availability – is a ferrous fumarate. In the recent years there has been introduced oral heme iron polypeptide with folic acid. Its enteric absorption exceeds 23 times that of ferrous fumarate preparations. It may be taken with or without meals [21]. Achlorhydria does not influence the absorption of this drug [22]. In the randomized trials ferrous sulphate in non-dialyzed patients was administered in a daily dose of 200 mg of the TID [23] or 325 mg of the TID [24].

Iron dextran, iron polymaltose, sodium gluconate and iron saccharate are the intravenous iron preparations. The molecules of these compounds are spherical and consist of trivalent iron – containing core and carbohydrate capsule consisting of micromolecular or macromolecular dextran, saccharose, polymaltose or gluconate. Iron is more easily released from low molecular compounds because iron saccharate and gluconate loosely bind with iron core. Iron dextran and iron saccharate are both available in Poland.

According to the Food and Drug Administration (FDA) the maximal single dose of intravenous iron is 100 mg of iron dextran, 125 mg of iron gluconate and 200 mg of iron saccharate. According to the EBPG recommended dose of intravenously administered iron during the first 6 months of treatment with the ESA it is 25–100 mg/week [3]. According to American guidelines the recommended dose is 25–150 mg/week [2]. The requirement is easily achievable in hemodialyzed patients, but not in a pre-dialysis period. The patients with CKD are potential candidates for renal substitution treatment, which in Poland consists in chronic hemodialysis requiring good vascular access in 90%. The vascular access protection by avoiding repetitive injections is substantial for planned renal substitution. Therefore, the importance of oral iron substitution and a nonstandard *i.v.* dose higher than 100 mg is emphasized. In these cases iron saccharate or gluconate is recommended because of fewer adverse events, especially the life-threatening ones [25,26]. The intravenous preparation of iron dextran is also used in the CKD patients [27]. Some investigators emphasize slower iron release from dextran complex and therefore this preparation prevents from an increase of the non-transferrin-bound iron (NTBI) level [28]. In clinical practice the usual total dose administered is 1000 mg with monitoring of the iron metabolism parameters. There are three methods of 1000 mg of iron gluconate *i.v.* administration:

- 1) bolus of 200 mg of undiluted drug in 2–5 min 5 times during 14 days,
- 2) intravenous infusion of 500 mg of drug diluted in up to 250 ml of 0.9% sodium chloride in 3.5–4 hours on days 1 and 14,
- 3) pulse injection of 200 mg every month in 5–12 months' treatment [29,30].

During the American Society of Nephrology (ASN) Meeting held in November 2006 the Canadian investigators reported the intravenous administration of 300 mg of iron saccharate in a period of 1 hour in non-dialyzed patients with absolute iron deficiency. The procedure was considered to be safe in the group of patients well tolerating a 2-hour iron saccharate infusion in the past [31]. After the initial test dose the iron dextran was infused intravenously in a dose of 1 g diluted in 500 ml 0.9% NaCl in a period of 6 hours. Non significant adverse events were observed in 4.9% of cases [27].

Recently conducted trials have shown that the ferumoxytol (the iron oxide particle coated with a carbohydrate capsule) can be used for rapid intravenous iron infusions (30 mg/sec) in non-dialyzed and peritoneal dialyzed patients. The iron doses of 255 mg and 500 mg were administered during 2 weeks and 1–2 weeks, respectively [32,33].

Iron administration efficacy

The substitution should provide a sufficient amount of iron in the organism to avoid or minimize the ESA administration. In non-dialyzed patients iron deficiency should be supplemented until reaching serum ferritin >100 ng/ml, hypochromic erythrocyte count <10%, the TSAT >20% or reticulocyte hemoglobin >29 pg/cell [1,2]. These minimal values should rise during treatment reaching, respectively, serum ferritin 200–500 ng/ml, hypochromic erythrocyte count <2.5%, the TSAT 30–40% and reticulocyte hemoglobin 35 pg/cell [1]. The efficacy of iron supplementation is evaluated by the hematocrit [23] and hemoglobin level elevation [27,30,33].

The efficacy of intravenous iron saccharate in a pre-dialysis period (1000 mg over the period of 5 months) was evaluated 1 month after the last dose. The absolute hematocrit elevation was 1.9%. It was noticed that the baseline serum ferritin and the TSAT were not always associated with a good erythropoietic response to treatment [29]. The intravenous administration of iron saccharate (12 doses of 200 mg every month) in the non-ESA treated patients showed to be effective. The iron supplementation allowed the increase of the Hb level from 9.7 ± 1.1 to 11.3 ± 2.5 g/dl. Along with hemoglobin, the iron and ferritin level and the TSAT increase was observed [30]. The authors estimate that intravenous iron administration allows ameliorating anemia in 36% of non-dialyzed patients. In the discussed trials diabetic patients were not included [30].

The intravenous administration of 1 g of iron to 56 non-dialyzed patients in a single dose resulted in the hemoglobin level increase by 1 g on average, and the ferritin level increase from 29.73 to 218.43 ng/ml (evaluated 12 weeks after the last iron dose). In 21 patients the mean ferritin level was still 136.5 ng/ml 1 year after the last iron dextran dose [27].

The intravenous administration of ferumoxytol resulted in the hemoglobin level increase by 1 g/dl on average in the period of 6 weeks after the administration of 1010 mg of iron. The maximal ferritin level – 931 ± 361 ng/ml – was achieved after 2 weeks. The adverse events (constipation, chills, formi-

cation, gastrointestinal symptoms, rash with itching) during ferumoxytol administration were few and mild [33].

Gotloib et al. [26] considered the beneficial intravenous administration of iron gluconate in the 250 mg twice a month dose during a period of 3 months in non-dialyzed patients without the ESA substitution. The mean hemoglobin level increased from 10.16 ± 1.32 g/dl to 11.96 ± 1.52 g/dl.

There are four randomized trials comparing the efficacy of intravenous and oral iron administration in non-dialyzed patients. Only one of them shows that the efficacy of oral administration is equal to intravenous administration efficacy [23]. The others demonstrate the superiority of intravenous therapy [24,34,35], although, according to Charytan et al. [34] intravenous iron administration is more efficient in the Hb rise above 11 g/dl but no more than by 1 g/dl. A significant predominance of *i.v.* administration was showed by Aggarwal et al. [35] in patients receiving the ESA in a pre-dialysis period. In patients receiving oral iron preparations the decrease of iron reserve was observed, while in those receiving intravenous preparations iron metabolism rates increased. Van Wyck et al. [24] investigated the efficacy of iron preparations in the treatment of the CKD patients from 35 towns who were in the third-fourth stage of the disease. Inclusion criteria were Hb ≤ 1 g/dl, the TSAT $\leq 25\%$ and the ferritin level ≤ 300 ng/ml. The patients did not receive the ESA, or the ESA dose remained unchanged during last eight weeks. The patients did not receive intravenous iron preparations during 6 months prior to the study. A divided dose of 1 g of intravenous iron saccharate (5×200 mg or 2×500 mg) during 14 days was administered in 79 of the included patients, and 82 of the patients were given oral iron sulphate in a dose of 325 mg (65 mg Fe^{2+}) 3 times a day for 56 days. On the forty-second day of the trial the mean increase of the Hb level was greater ($p = 0.03$) in patients receiving intravenous iron preparations (0.7 g/dl) than in those receiving oral preparation (0.4 g/dl). Moreover, 60% of *i.v.* treated patients reached the Hb ≥ 11 g/dl comparing with 43% of the orally treated. The increase of hemoglobin level above 1 g/dl was confirmed in a greater percentage of patients ($p = 0.03$) treated intravenously (44.3%) than in those treated orally (28.0%).

Iron preparations should not be administered in infectious and non-infectious inflammatory conditions because they may be intensified by non-transferrin bound iron (NTBI).

Vitamins in iron substitution

Vitamin C increases iron mobilization from ferritin and the reticuloendothelial system and its use in the process of hem production [36,37]. It is administered orally to enhance the absorption of iron. Supplementation in the case of a low vitamin C level may also intensify the antioxidant effect of vitamin E [1]. It is especially significant when administered intravenously because of the prooxidant effect of the free intravenous iron. Notwithstanding, a high dose of vitamin C has

the prooxidant effect as well – directly or through iron release [38,39].

High doses of vitamin C ameliorate the response to the ESA in patients with functional iron deficiency [40,41], but that treatment may predispose the CRD patients to the oxalosis [1,2].

According to the American data high doses of vitamin C in anemia treatment of the CRD patients are not recommended [2].

Iron side effects

The most frequent symptoms of iron intolerance are skin irritation (32.3%), allergic dermatitis (15.4%), dyspnoea (13.8%), urticaria (11.5%) and back pain (10.8%) [42]. Gastrointestinal disturbances were observed both during intravenous (17.6%) and oral (11.5%) iron administration [24]. The intensity of hypotension observed during intravenous administration depended on the drug dose and administration rapidity. Hypotension was observed in 6.7% of patients receiving iron saccharate intravenously, particularly when a single dose of 500 mg was administered [24].

Other potentially dangerous side effects are: anaphylaxis, the increase of the NTBI serum level, increased infection susceptibility, enhanced inflammation reactions and the aggravation of sepsis symptoms, the increase of oxidative stress (kidney damage, endothelium damage with atherosclerosis acceleration) and iron overload. The anaphylactic reactions were mainly described when iron dextran was administered. Iron dextran is less expensive and more available in hospitals. In the case of patients with allergy to dextran, the gluconate or saccharate iron may be considered. The frequency of other than allergy symptoms incidence was similar in the group of patients sensitized to dextran ($n = 144$) and in the group of well tolerating patients ($n = 2173$), and it was 11.1% and 12.3% respectively. Serious adverse events were observed in the two groups with similar frequencies (0.7% and 0.6% respectively) [43].

Initially the NTBI was diagnosed only in the TSAT patients = 100% [44]. More sensitive tests (catalytic bleomycin reaction) can diagnose the NTBI in the TSAT <100%. The increased NTBI was noticed in a rapid *i.v.* infusion of >100mg of iron saccharate. The lower plasma volume (low body mass) can promote the free iron activity revealing [24,45,46].

The NTBI is used by a microorganism for its growth, e.g. *Staphylococcus epidermidis*. In the IHD (intermittent hemodialysis) patients there was the intense *Staphylococcus epidermidis* growth observed 5 minutes after the 100 mg of iron saccharate administration comparing with healthy volunteers. The addition of apotransferrin to the IHD patients serum prevented the *Staphylococcus epidermidis* growth [47]. This observation leads to the conclusion that the low transferrin serum level may promote the pro-infection activity of the free iron.

In the case of the iron overload, discontinuation of the iron administration and more effective iron utilization stimulated by the ESA are recommended. The chelating agents are less

commonly used also because of their potential pro-infection activity.

Nephrotoxicity of iron

In the pre-dialysis period the nephrotoxicity of iron preparations need to be considered. In 1999 Silverberg et al. [48] described the group of non-dialyzed patients ($n = 12$) receiving iron *i.v.* during the treatment with erythropoietin in the cumulative dose of 1–2 g in 4 months. In a 12-month follow-up neither proteinuria nor increased oxidation of the LDL exponents were observed [48]. The 2004 study by Agarwal et al. [49] concerning patients with the GFR <60 ml/min showed that *i.v.* iron saccharate administration instantly increases the oxidizing stress followed by transient proteinuria and renal tubule damage. The cytotoxicity of iron preparation on endothelial cells is caused by mitochondrial dysfunction [28] or the DNA damage [50] followed by proliferation suppression.

In the other clinical trials the GFR modification by the MDRD (The Modification of Diet in Renal Disease) test in non-dialyzed patients treated with intravenous and oral iron preparations was showed. The GRF decrease was significant ($p = 0.0100$) after oral iron administration [24]. The unfavorable impact of iron intravenous administration in the total dose of 2.4 g per year on the GFR, systolic or diastolic blood pressure was not shown by Mircescu et al. [30]. The authors suggest that intravenous iron administration in anemia of the CRF patients slows down the chronic kidney failure progression.

SUMMARY

In non-dialyzed patients, iron supplementation is provided orally in most cases. Intravenous therapy is necessary in the cases of significant iron deficiency, intestinal malabsorption, oral preparations intolerance and during treatment with the ESA. Iron administration in a single intravenous dose exceeding 100–200mg remains an experimental method. In the CRF patients the adverse events of iron preparation, especially nephrotoxicity, should be considered.

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