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A primer on iron therapy

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Introduction

Iron deficiency is a frequent complication in patients with chronic kidney disease (CKD). Major causes are reduced dietary intake, impaired absorption, chronic blood loss, inflammatory or infectious comorbidity and increased requirements during correction of renal anaemia with erythropoiesis-stimulating agents (ESA). Inadequate iron stores with reduced availability of iron to the bone marrow are the main cause of hyporesponsiveness to ESA treatment. Thus, in the vast majority of haemodialysis patients, intravenous iron is used in combination with ESA to treat renal anaemia. Optimal iron management, therefore, includes the monitoring of iron status and the supplementation of adequate amounts of iron, to maintain haemoglobin levels at target in a cost-effective manner [1].

Monitoring iron status

Ferritin

Serum ferritin is a parameter of iron storage in the reticuloendothelial system. In subjects without kidney disease, a value below 15 ng/ml indicates absolute iron deficiency [2]. In CKD patients, absolute iron...
deficiency is already considered when ferritin levels are <100 ng/ml [3]. According to the K/DOQI guidelines the optimal ferritin target is 100–500 ng/ml in ESA-treated CKD patients and 200–500 ng/ml in patients maintained on haemodialysis [4]. Administration of intravenous iron may result in a transient increase in serum ferritin. Therefore, before measuring ferritin, an interval of 1 week should be observed after intravenous administration of 100 mg of iron sucrose or of 62.5 mg of ferric gluconate and 2–4 weeks when 500–1000 mg of iron dextran are given. Inflammatory conditions, severe infections, liver disease and malignancies may give rise to enhanced serum ferritin levels irrespective of iron storage. Ferritin levels should be determined every 3 months in CKD patients to monitor iron storage.

**Transferrin saturation (TSAT)**

Transferrin saturation is a measure of the amount of iron bound to plasma transferrin. Normal values range between 20% and 45%. High values (>90%) are observed in haemochromatosis, low values (<20%) may indicate insufficient iron supply to the bone marrow. In ESA-treated patients, iron supplementation might be started once the TSAT falls below 20%. High-dose ESA therapy for rapid correction of anaemia may result in low TSAT levels, even in the presence of normal iron stores. This condition—low TSAT and normal ferritin values—is referred to as functional iron deficiency. Functional iron deficiency may also occur during infection or inflammation [3]. Supplementation of vitamin C (200 mg per day orally or 300–500 mg intravenously after each haemodialysis session) may result in the release of iron from the reticuloendothelial system, and thereby ameliorate hyporesponsiveness to ESA [5].

**Hypochromic red cells**

The percentage of hypochromic red cells in the circulation is a direct parameter of iron supply to the bone marrow. In healthy subjects, hypochromic red cells are below 2.5%. Values above 10% indicate iron-deficient erythropoiesis. During ESA therapy, hypochromic red cells may reach values of 50% and more in cases of prolonged iron-deficient erythropoiesis [6].

The measurement of hypochromic red cells may not be available, as it requires the Technikon H*3 or ADVIA-120 haematology system, which both measure cell size and haemoglobin content in individual red cells by flow cytometry. Blood samples (EDTA blood) are stable for 24 h and can be shipped without cooling.

**Content haemoglobin of the reticulocyte (Chr)**

Modern haematology analysers are also able to analyse reticulocytes, both in terms of cell volume (MCVr) and haemoglobin content (Chr). Using the Technikon H*3 System, a Chr value <29 pg/cell indicates iron-deficient erythropoiesis. Chr is a direct indicator of iron availability to the marrow [7]. Using the ADVIA 2120 and the Sysmex XE 2100 analyzers in 1500 dialysis patients, Brugnara et al. [8] defined a cutoff for reticulocyte haemoglobin content at 27 pg/cell with a sensitivity of 93% and a specificity of 83%. In the presence of functional iron deficiency, the determination of hypochromic red cells or Chr might be used to decide whether iron supplementation should be initiated [9].

**Iron therapy**

**Iron requirements**

For anaemia correction, 150 mg iron is required to increase haemoglobin concentration by 1 g/dl. In haemodialysis patients, iron requirements due to blood loss during dialysis is estimated to be in the range of 1−3 g/year. In most cases, iron substitution in such quantities is only possible by intravenous administration, as higher doses of oral iron are associated with considerable intestinal side effects. Iron requirements in CKD, renal transplant and peritoneal dialysis patients are lower than in haemodialysis patients. In general, anaemia is less severe and iron deficiency less pronounced. Thus, patients might begin with oral iron (100–200 mg/day) and only if iron status does not improve or intolerable side-effects occur, iron might be administered intravenously.

**Choice of intravenous iron preparations**

There are three different parenteral iron preparations available in most European countries: Iron-(III)-gluconate (Ferrlecit®), iron-(III)-hydroxide-sucrose (Venofer®) and iron-(III)-hydroxide-dextran (Cosmofer®). These formulations differ in terms of complex stability and incidence of adverse reactions. Iron dextran and iron sucrose are more stable than ferric gluconate, which translates directly into the maximal single doses that can be administered: Cosmofer® 20 mg/kg body weight; Venofer® 500 mg; Ferrlecit® 62.5 mg [10–12]. Iron dextran preparations on the other hand may cause life-threatening anaphylactic reactions. According to Chertow et al. [13], the rates of life-threatening events were 6 (iron sucrose), 9 (ferric gluconate) and 33 (iron dextran) per 10 million administrations, respectively. In the analysis of Bailie et al. [14], the rates of fatal events were 14 with iron dextran, six with ferric gluconate and zero with iron sucrose. Taken together, life-threatening and fatal events are most frequent with the use of iron dextran. Iron sucrose carries the lowest risk for severe adverse events [14]. Anaphylactoid reactions have predominantly been reported with the use of iron dextran [15]. For these reasons, the Revised European Best Practice Guidelines do not recommend the use of iron dextran formulations [16].
Dosing of intravenous iron preparations

For the correction of anaemia in haemodialysis patients, the dosage of intravenous iron should amount to a total of 1000 mg, given over a period of 6–12 weeks to ensure adequate iron supply for the ESA-stimulated erythropoiesis. Iron requirements during the maintenance phase of anaemia may vary considerably, depending to a large degree on the amount of blood lost during dialysis. Dosing might vary, from small amounts of ferric gluconate (10–20 mg) given at each dialysis treatment, to the administration of a large single dose of iron sucrose (250 mg) once every 4 weeks [17]. Intravenous iron has been linked to the occurrence of infections, systemic inflammation, tissue oxidation and atherosclerosis. A recent multicentre trial by Aronoff et al. [18], however, demonstrated that iron sucrose is safe when given in iron-deficient patients or for maintenance of iron stores.

As anaemia is usually less severe in pre-dialysis and peritoneal dialysis patients, iron requirements are usually lower than in patients maintained on haemodialysis. Renal transplant recipients may also suffer from iron deficiency. Iron requirements are much less in these patients during ESA therapy; thus iron might be given orally. However, intravenous iron has been reported to be much more effective than oral supplementation [19,20].

Summary

The incidence of iron deficiency is high in CKD patients. Serum ferritin and TSAT are used as routine diagnostic parameters for the assessment of iron status in CKD patients, with and without ESA therapy. The measurement of hypochromic red cells or reticulocyte haemoglobin content can be helpful with the decision whether to administer intravenous iron in functional iron deficiency. Ferritin should be measured four times per year in CKD patients. According to the K/DOQI guidelines, target values for ferritin are 200–500 ng/ml in dialysis patients and 100–500 ng/ml for CKD patients. TSAT is recommended to be about 20–40%.

Iron requirements in pre-dialysis and peritoneal dialysis patients are lower than those of haemodialysis patients. However, most CKD patients eventually have to be treated with intravenous iron, as oral agents are not tolerated because of gastrointestinal side effects. Iron therapy should also be discontinued during acute bacterial infections, since iron may stimulate the growth of micro-organisms. Due to a higher risk of infection, intravenous iron substitution should be performed conservatively in patients with permanent dialysis catheters. Patients with chronic inflammatory disorders (e.g. rheumatoid arthritis, Crohn’s disease) may receive intravenous iron therapy at normal dosage and frequency. For safety reasons, only dextran-free iron formulations should be administered, as the incidence of severe adverse events (anaphylactoid reactions) is lower than with iron dextran preparations.

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