Iron monitoring and supplementation: how do we achieve the best results?

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Abstract A number of factors have been shown to limit the response to recombinant human erythropoietin (r-HuEPO). One major factor appears to be an inadequate iron supply to the bone marrow. Erythropoiesis is dependent upon a continuous supply of iron to the bone marrow. The rate at which iron can be drawn from existing stores may easily limit the rate of delivery for haemoglobin synthesis. This results in ‘functional iron deficiency’ which is distinct from ‘absolute iron deficiency’ caused by depletion of iron stores. At present there are three main parameters available to clinicians wishing to monitor iron status in their patients: serum ferritin and transferrin saturation (TFS), which are indirect measurements, and the percentage of hypochromic red cells, which directly reflects marrow iron status. Ferritin levels should be measured before starting r-HuEPO therapy to ensure adequate iron stores (>200 µg/l), and when patients move from the correction phase to the maintenance phase of therapy (have stores become depleted during the correction phase?). In addition, ferritin levels can give an indication of iron overload following excess parenteral iron administration. The TFS represents a balance between iron supply by stores and demand by bone marrow. A saturation below 20% probably indicates iron-deficient erythropoiesis. However, this is an indirect measure of marrow iron supply and wide fluctuations have been observed when determined at different time points. The percentage of hypochromic red blood cells is measured by flow cytometry and a hypochromic subpopulation of more than 10% (normal percentage <2.5%) indicates iron-deficient erythropoiesis. However, not all departments may have access to the required equipment. The aim of iron supplementation is to provide sufficient iron for the correction phase and to replace iron losses (1500–2000 mg/year in haemodialysis patients) during the maintenance phase of r-HuEPO therapy. This amounts to a daily iron need in the range of 5–7 mg, which is well above the normal dietary intake and absorptive capacity of the human intestine. Therefore, there is a need for intravenous iron, in particular when the patient has absolute or functional iron deficiency, is intolerant of oral iron, or is not complying well with the oral regimen.

Key words: ferritin, hypochromic red blood cells, iron, r-HuEPO, transferrin saturation

Introduction

Since the introduction of recombinant human erythropoietin (r-HuEPO) it has become apparent that adequate iron supply to the bone marrow is essential for a satisfactory haematopoietic response. This is particularly important because large quantities of r-HuEPO may be wasted, which impacts on the cost-effectiveness of this treatment. Based on the literature, 80–90% of dialysis patients on r-HuEPO will require iron at some stage in their therapy. The majority of haemodialysis patients is treated with intravenous iron, while most continuous ambulatory peritoneal dialysis (CAPD) and pre-dialysis patients are treated with oral iron, because of lower iron needs and the practicality of achieving intravenous access.

Monitoring iron stores

Serum ferritin

Serum ferritin (S-ferritin) provides a measurement of storage iron. Normal values are 20–100 µg/l in females and 30–300 µg/l in males. Approximately 100 µg/l S-ferritin represents 1 g of storage iron [1]. The minimal S-ferritin required in uraemic patients for response to r-HuEPO is above 200 µg/l according to Allegra et al. [2]. In patients on intravenous iron, S-ferritin should be determined several times per year as a measure of iron stores, in order to exclude iron overload. One has to bear in mind, however, that S-ferritin will be elevated during parenteral iron therapy. For this reason, it is advisable to determine S-ferritin 3–6 weeks (depending on the dose of iron) after the last iron administration. During long-term parenteral iron
therapy, one should be cautious not to raise S-ferritin above 500 µg/l (equivalent to 5 g of storage iron), because above this threshold iron is being stored progressively outside the reticulo-endothelial system. In fact there are a number of reports in the literature that describe abnormalities in granulocyte function, such as impaired phagocytosis and intracellular killing in iron overloaded dialysis patients [3,4], leading to an increased incidence of bacterial infections [5].

Transferrin saturation

The transferrin saturation (TFS) is a measure of the iron content of transferrin, the only protein in the plasma that transports iron from the stores to the bone marrow. One has to bear in mind, however, that the TFS provides no information on iron stores or utilization of iron by the bone marrow. Values below 20% are considered to be associated with suboptimal delivery of iron to the marrow, in particular during pharmacological stimulation of erythropoiesis by r-HuEPO. Values below 20% may even be seen in the presence of normal or high S-ferritin values, indicating functional iron deficiency [6]. Functional iron deficiency may occur during high-dose r-HuEPO therapy or in the presence of an acute phase reaction. Recent recommendations regarding iron supplementation suggest treating functional iron deficiency with intravenous iron in those cases where an acute bacterial infection can be excluded [7].

Percentage of hypochromic red blood cells

Hypochromia is defined as an individual red cell haemoglobin concentration below 28 g/dl and is measured by flow cytometry. A hypochromic red blood cell (RBC) subpopulation of less than 2.5% is considered normal, while values above 10% indicate iron-deficient erythropoiesis [8]. Long-standing iron-deficient erythropoiesis during r-HuEPO therapy may result in hypochromic RBC subpopulations of more than 50% [9]. Hypochromic RBCs are highly sensitive for detecting iron-deficient erythropoiesis, but this parameter can only be obtained by using certain types of haematology analysers (Technikon H1-, H2- or H3-Systems; Bayer Diagnostics, Munich, Germany), which are able to determine the haemoglobin concentration in individual RBCs.

It has to be emphasized, however, that uraemic patients not on r-HuEPO may have a normal percentage of hypochromic RBCs despite reduced iron stores and/or low transferrin saturations, due to their hypogenerative type of anaemia. Once r-HuEPO therapy is started and erythropoiesis is stimulated, huge numbers of hypochromic RBCs will be released within a few days into the circulation [9]. Thus, this parameter is a direct measure of the relationship between iron availability to, and iron demand of, the bone marrow.

Reticulocyte haemoglobin content

Using the H3-System, the reticulocyte haemoglobin content (CHr) can be determined in individual reticulo-cytes, averaging 26 pg/cell in healthy individuals. Recently, Fishbane et al. [10] showed that dialysis patients have normal CHr values (27.5±2.8 pg/cell). Values below 26 pg were highly predictive of iron-deficient erythropoiesis. Within 48 h after the intravenous administration of 1000 mg of iron dextran, the majority of these patients responded with an increment in their CHr values. If these findings can be corroborated by other authors, this parameter may turn out to be a helpful tool to diagnose iron-deficient erythropoiesis.

RBC zinc protoporphyrin

When iron availability is reduced during haem synthesis, zinc instead of iron is incorporated into the protoporphyrin molecule. During adequate iron availability, zinc protoporphyrin (ZnPP) concentrations in RBCs are below 40 µmol/mol haem. Values above 90 µmol/mol haem are considered to indicate iron-deficient erythropoiesis (or lead intoxication). As with hypochromic RBC populations and CHr, ZnPP represents a direct measure of iron availability to the marrow. A major difference, however, is that ZnPP is determined in the whole RBC population of the respective sample, rather than a subpopulation. Based on the relatively long life span of RBCs in the circulation, ZnPP integrates information on iron availability over a prolonged period of time (similar to HbA1c in diabetes mellitus). In the clinical setting, Haskka et al. [11] showed that ZnPP values above 100 µmol/mol haem correctly identified iron-deficient erythropoiesis in nine out of 10 dialysis patients on r-HuEPO, as measured by their response to intravenous iron. On the other hand, Braun et al. [12] were not able to corroborate these findings. What is more, there is a significant number of patients displaying ZnPP values between 50 and 100 µmol/mol haem, who may or may not respond to intravenous iron [13]. In summary, the measurement of ZnPP seems to provide less timely information of iron availability to the bone marrow as compared with hypochromic RBCs. Its use may be recommended when the other parameters are not available.

Iron therapy

Need of iron in haemodialysis patients

The aim of iron therapy is to provide sufficient iron for both the correction and maintenance phases of r-HuEPO therapy. The fact that it will take 150 mg of iron to synthesize 1 g of haemoglobin can be used to approximate the amount of iron necessary for haem synthesis during the correction phase. Once the target haematocrit is reached, the aim of iron supplementation is to substitute for losses during extracorporeal therapy, which may amount to up to 2 g of iron per year [14]. For most patients, such quantities of iron can only be administered parenterally, because oral iron, particularly in higher doses, is accompanied
by significant intestinal side effects in most individuals. The major long-term risk associated with intravenous iron is overload, which may easily be prevented by monitoring S-ferritin values.

Need of iron in pre-dialysis and CAPD patients

Both pre-dialysis and CAPD patients frequently have higher baseline haemoglobin levels compared with haemodialysis patients and the loss of iron is much less pronounced. Therefore, the need for iron is lower in these two groups of patients, during both the correction and maintenance phases. It is for these reasons, together with the practicality of gaining venous access, that many nephrologists start these patients on a course of oral iron. Only those who do not tolerate this form of therapy, or who cannot be supplemented adequately, are then switched to intravenous iron. In such patients, iron dextran and iron saccharate should preferably be used, as both compounds can be given safely in higher doses (fewer injections necessary). Furthermore, due to their relatively high molecular weight, they are not filtered by the glomerulus and thereby cannot exert any potential tubulotoxic side effects.

Iron preparations

Safety of intravenous iron preparations

In continental Europe there are presently two different iron preparations available: iron-(III)-gluconate and iron-(III)-hydroxy saccharate, while in the UK both iron hydroxy saccharate and iron dextran are available, and in North America iron dextran is almost exclusively used. In terms of safety, two major aspects must be considered. 1) With the administration of iron dextran there is a distinct possibility of anaphylactic reactions due to preformed antibodies to dextran. According to Hamstra et al. [15] the rate of severe immediate reactions is approximately 0.1% of administrations, which is low but still requires the administration of a test dose followed by careful patient observation. 2) While there are practically no anaphylactoid reactions with iron gluconate and iron saccharate, both compounds may release small amounts of iron from the complex which may lead to acute iron toxicity, particularly when higher doses are administered. This is especially pronounced with the use of iron gluconate. Zanen et al. [16] have found oversaturation of transferrin, that is a saturation above 100%, after rapid injection of 62.5 mg iron gluconate, while administration of 100 mg of iron saccharate apparently does not result in oversaturation of transferrin [17].

These observations may explain episodes of acute toxicity after administration of iron gluconate, but not with the use of iron saccharate or iron dextran. Thus, the maximum single doses recommended by the manufacturers are 62.5 mg for iron gluconate, 200 mg for iron saccharate and 1000 mg for iron dextran. In the clinical setting most centres prefer to inject lower single doses, such as 100 mg [18] or 200 mg [19] of iron saccharate or 100 mg of iron dextran [20].

Efficacy of intravenous iron preparations

While iron dextran can be given in relatively high single doses, there is a delay before iron is available to the bone marrow. This is due to processing in the reticuloendothelial system, which is necessary to liberate iron from the complex. Thus, Macdougall et al. [21] found that ferritin did not rise until 4–7 days after administration of iron dextran, while after injection of iron saccharate, ferritin levels had already increased after 24–48 h.

Conclusion

Absolute and functional iron deficiency are probably the most frequent causes of r-HuEPO resistance. The diagnostic evaluation of iron status includes S-ferritin levels, TFS and percentage of hypochromic RBCs (when available). The combination of these three parameters allows for exact characterization of iron metabolism in the majority of patients with renal failure. S-ferritin values below 200 μg/l suggest absolute iron deficiency, while in functional iron deficiency there is a low TFS (<20%) and an increased percentage of hypochromic RBCs (>10%).

Adequate iron therapy in iron-depleted haemodialysis patients may result in a considerable reduction of the r-HuEPO dose. Intravenous iron supplementation is recommended in haemodialysis patients during both the correction and maintenance phases of r-HuEPO treatment. In most countries, the choice of iron complex will depend on the iron preparation available. In pre-dialysis and CAPD patients (without absolute iron deficiency), oral iron therapy may be feasible, as renal anaemia is frequently less severe and the loss of iron less pronounced compared with haemodialysis patients.

References