Adjunctive therapy in anaemia management

Walter H. Hörl

Division of Nephrology and Dialysis, Department of Medicine III, University of Vienna, Vienna, Austria

Abstract
Iron supplementation is essential for adequate response to recombinant human erythropoietin (rHuEPO) or darbepoetin alfa. Oral iron therapy is often ineffective as the quantity of iron absorbed after oral intake may be insufficient to keep pace with the demands of rHuEPO-stimulated erythropoiesis in patients with end-stage renal disease (ESRD). Currently available i.v. iron preparations include dextran, iron gluconate, and iron sucrose. As rare, but serious, adverse reactions to i.v. iron dextran have been reported, alternative preparations may be preferred. Careful monitoring of iron parameters is required to avoid the effects of over-treatment. Renal anaemia and iron therapy are associated with oxidative stress, leading to a shortening of the lifespan of red blood cells (RBC) and resistance to rHuEPO. rHuEPO therapy may also enhance oxidative stress on RBC. Oxidative stress can be attenuated or prevented by supplementation with vitamin E or melatonin. Vitamin E therapy has also been shown to have a rHuEPO-sparing effect. Disturbances of carnitine metabolism may contribute to the development of renal anaemia in ESRD patients. Oral or i.v. L-carnitine therapy results in an increase in haematocrit and a significant decrease in rHuEPO requirement in HD patients. As yet, there is no general recommendation for L-carnitine supplementation for ESRD patients with renal anaemia.

Keywords: anaemia; carnitine; chronic kidney disease; erythropoietin; iron; oxidative stress; vitamin E

Introduction
Adjunctive therapies that potentially enhance the effectiveness of recombinant human erythropoietin (rHuEPO) or darbepoetin alfa in patients with chronic kidney disease (CKD) include iron and vitamin supplementation, L-carnitine, androgens, adequacy of dialysis and nutrition, and/or certain cytokines [1]. Data on iron, vitamin E, and L-carnitine supplementation in patients with CKD are summarized here.

Iron and renal anaemia
Patients on maintenance therapy with rHuEPO or darbepoetin alfa frequently develop iron-deficient erythropoiesis. This can result from depletion of iron stores (absolute iron deficiency) or from failure to deliver adequate iron to the bone marrow despite apparently appropriate iron stores (functional iron deficiency). Absolute iron deficiency in patients with end-stage renal disease (ESRD) is defined as serum ferritin <100 μg/l. In contrast, functional iron deficiency is characterized by normal or high serum ferritin levels, but low transferrin saturation (TSAT <20%) and/or elevated percentage of hypochromic red blood cells (% HRC; >10) [2].

Fishbane et al. [3] randomized maintenance haemodialysis (HD) patients to one of two study groups. For patients in group 1, iron management was based on measurement of serum ferritin and TSAT, and in patients of group 2, iron management was based on measurement of reticulocyte haemoglobin (Hb) content (CHr). The authors demonstrated that CHr <29 pg is a markedly more stable parameter than serum ferritin or TSAT. CHr may be particularly useful in cases where serum ferritin exceeds 500 μg/l but TSAT <15%, and in patients with elevated levels of C-reactive protein. Furthermore, the cost of measuring CHr is significantly lower than that of conventional iron indices [4].

I.v. iron supplementation
Currently available i.v. iron preparations include iron dextran, iron gluconate, and iron sucrose. Life-threatening anaphylactic reactions can occur with iron dextran, even at test doses. Such reactions are due to an immune-mediated response in patients who have...
dextran antibodies. The lack of a reaction to a test dose does not ensure that the patient will not experience a reaction in the future.

Fletes et al. [5] investigated the incidence of suspected iron dextran-related adverse events in clinical practice. The authors concluded that serious adverse reactions to i.v. iron dextran are rare in clinical practice, and that the risk appears to depend on the specific formulation administered. However, when considering the overall risks, potential benefits, and relative costs, they questioned the benefits of alternative (non-dextran) preparations of i.v. iron.

According to Macdougall [6], dextran-containing iron compounds should be used only when absolutely necessary. Use of a test dose for iron sucrose or iron gluconate was not recommended, as there are no documented antibodies against these compounds. Furthermore, in over 40 years of use, no fatalities have been reported with i.v. iron sucrose and iron gluconate (in contrast to iron dextran).

A study by Prakash et al. [7] assessed the efficacy and safety of very large doses of iron dextran or sucrose in patients receiving peritoneal dialysis (PD). Providing the patients remained asymptomatic after a test dose (25 mg of iron dextran or sucrose dissolved in 50 ml normal saline infused over 30 min), they received 475 mg of iron dextran or sucrose over 4–5 h. Two anaphylactic reactions were observed, one in a patient receiving iron dextran and one in a patient receiving iron sucrose. It is unclear as to whether it was the large dose, or the formulation of the iron sucrose preparation, that caused the adverse reaction in the latter case.

According to Chandler et al. [8] iron sucrose doses up to 300 mg may be safely given over 2 h, but doses of 500 mg should be administered as an infusion over 3.5 h or longer [6].

**Oral iron supplementation**

In patients with renal anaemia, oral iron therapy is often ineffective in maintaining adequate iron stores. In particular, the quantity of iron absorbed after oral intake may be insufficient to keep pace with the demands of rHuEPO-stimulated erythropoiesis in patients with ESRD. Kooistra et al. [9] found that mucosal iron uptake, mucosal iron transfer, and iron retention were significantly lower in non-uraemic iron-deficient population. These parameters were also observed to be significantly lower in iron-replete HD patients than in iron-replete controls. High levels of C-reactive protein are associated with low iron absorption in HD patients. Mucosal iron uptake, mucosal iron transfer, and iron retention are also significantly lower in PD patients than in controls [10]. Dittrich et al. [11] observed no significant difference in the increase in serum iron after oral intake of four iron sulphate tablets (105 mg elemental iron per tablet) between PD patients and healthy subjects. However, iron absorption was significantly greater in PD patients with absolute iron deficiency compared with those with functional iron deficiency. Iron-replete PD patients showed the lowest iron absorption, indicating that a high dose of oral iron did not prevent the bowel’s ability to reject unneeded iron. Side effects, such as nausea and vomiting, occurred more frequently during high-dose oral iron supplementation in control subjects than in PD patients (20 vs. 8.8%). In short, i.v. iron therapy is more effective than oral iron supplementation [12] in achieving and maintaining adequate iron stores in patients with renal anaemia.

**Oxidative stress and renal anaemia**

Plasma levels of lipid peroxidation products correlate with the severity of renal anaemia. A decrease in red blood cell (RBC) count is accompanied by a deficiency of reduced glutathione (GSH) and of enzymes that metabolize lipid peroxidation products. This results in the diminished antioxidative capacity of blood in uraemic patients [13]. Correction of renal anaemia with rHuEPO results in a decrease of malondialdehyde (MDA) levels and 4-hydroxynonenal concentrations. In addition, the availability of antioxidants, reflected by enhanced superoxide dismutase and GSH peroxidase activities, increases after correction of renal anaemia [14]. The data suggest that the anaemic state itself contributes to free radical production [15].

Erythrocyte membrane lipid peroxidation occurs in patients with CKD [16]. Serum albumin inhibits peroxidation of erythrocyte membrane lipids. Persistent hypoalbuminaemia worsens the serum antioxidant activity contributing to increased oxidative cell damage in uraemia [17].

Exogenous reduced GSH administration results in improved RBC survival in HD patients [18]. Correction of renal anaemia also improves the antioxidant system. Ludat et al. [19] compared MDA, GSH, and glutathione disulphide (GSSG) levels in HD patients with haematocrit (Hct) < 30, 30–39, and ≥40%. MDA levels were significantly lower in the group with normal Hct compared with the other two groups. GSH and GSSG whole-blood levels in HD patients with Hct ≥40 and 30–39% were significantly higher than in HD patients with Hct <30%. A substantial part of oxidative stress in patients with ESRD is due to renal anaemia. Thus, treatment of renal anaemia may effectively reduce oxidative stress in these patients.

Lipid peroxidation of the RBC membrane may result in resistance to erythropoietin due to enhanced haemolysis caused by oxidative stress. Gallucci et al. [20] investigated the degree of RBC membrane oxidative damage in HD patients who failed to respond to maximal rHuEPO therapy. In these patients, RBC MDA, reticulocyte count, plasma-free Hb and serum lactate dehydrogenase were significantly higher, while plasma haptoglobin was significantly lower, compared with HD patients who showed a good response to
standard rHuEPO therapy, or with HD patients not requiring rHuEPO treatment.

Lipid peroxidation of the RBC membrane by free radicals and subsequent impaired RBC deformability and splenic sequestration may be involved in ageing and lysis of RBCs. Thus, oxidative stress contributes to the shortened survival of RBCs. Treatment with rHuEPO was observed to significantly rejuvenate RBCs. However, no significant improvement in the RBC oxidative sensitivity, RBC deformability, splenic RBC volume, slow mixing splenic RBC volume, and intrasplenic RBC transit time was observed with rHuEPO therapy [21]. Correction of renal anaemia by rHuEPO enhances oxidative stress on RBCs [22,23]. Türi et al. [24] reported the pro-oxidant effect of rHuEPO therapy on the GSH redox system and Hb oxidation in children on maintenance HD. Adjuvant vitamin E therapy alleviated the rHuEPO-induced oxidative stress. The high ratio of GSSG/GSH (an indicator of oxidative stress) to level carboxyhaemoglobin (an indicator of haemolysis) was decreased by oral vitamin E (15 mg/kg/day). Furthermore, the combination of rHuEPO and vitamin E therapy increased Hb and Hct values significantly earlier than rHuEPO therapy without vitamin E [25]. Data from Cristol et al. [26] have also demonstrated that vitamin E supplementation has a sparing effect on rHuEPO dosage requirement in HD patients.

Oxidative stress and iron therapy

Loughrey et al. [27] have reported that i.v. iron supplementation may contribute to increased free radical production. Redox-active iron is a potent pro-oxidant. Hydroxyl radicals and lipid alkoxyl radicals are formed by the Fenton reaction. These reactive oxygen species trigger iron-induced lipid peroxidation in the presence of hydrogen peroxide or lipid hydroperoxides [27–31]. Vitamin E is a potent antioxidant that inhibits lipid peroxidation [32,33]. Roob et al. [34] showed that a single dose of vitamin E (1200 IU) attenuated lipid peroxidation in maintenance HD patients receiving i.v. iron. Acute oxidative stress generated during infusion of 100 mg iron sucrose and rHuEPO, can be prevented by a single oral dose of melatonin (0.3 mg/kg) [35].

Carnitine and renal anaemia

Disturbances of carnitine metabolism may contribute to the development of renal anaemia in patients with ESRD. A beneficial effect of carnitine supplementation on renal anaemia has been reported both before [36–39] and after [40–43] the introduction of rHuEPO therapy.

Oral or i.v. 1-carnitine therapy results in an increase in Hct [36,38], 1-carnitine may enable stabilization of the erythrocyte membrane by facilitating the uptake of structural lipids [44]. There is a significant negative correlation between haemolysis and serum levels, total and free carnitine, suggesting reduced erythrocyte fragility in HD patients and in patients with carnitine deficiency. There is also a significant negative correlation between rHuEPO requirement and serum levels of total and free carnitine [45]. 1-carnitine supplementation results in an increase of erythrocyte Na+/K+-ATPase [37] and in an improvement of erythrocyte membrane fragility [46]. However, there is also a negative correlation between erythrocyte fluidity and rHuEPO requirement suggesting a role of anaemia on erythrocyte membrane fragility per se [47].

Labonia [41] reported a significant decrease in rHuEPO requirement in carmine-treated HD patients. They found a decrease in rHuEPO requirement in eight out of 19 HD patients treated with i.v. 1-carnitine in combination with i.v. iron sucrose. In these eight patients, the weekly rHuEPO dose decreased by 36.9 ± 23.3%. However, when all 19 patients were compared before and after 4 months of 1-carnitine supplementation, the rHuEPO requirement remained unchanged [48].

Conclusions

Iron supplementation is essential for adequate response to rHuEPO or darbepoetin alfa. Optimal monitoring of iron parameters is required to avoid over-treatment with iron. Renal anaemia and iron therapy are associated with oxidative stress, which can be attenuated or prevented by vitamin E or melatonin. Vitamin E also has a rHuEPO-sparing effect. There is no general recommendation for 1-carnitine supplementation for patients with ESRD and renal anaemia.

References

Adjuvant therapy in anemia management


