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IRON METABOLISM

Iron overload and chelation

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Abstract
Iron is one of the most common elements in nature. As a transition metal it is very efficient in electron transport and redox reactions. The proteins and enzymes in which iron is an essential component play a key role in respiration, energy production, detoxification of harmful oxygen species and cell replication. Despite the abundance of iron in nature, the solubility of its stable ferric form is extremely low. Hence, living organisms were compelled to develop efficient mechanisms for iron transport and storage.

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Iron homeostasis

In recent years a number of key mechanisms have been described which are responsible for adaptation to changing environmental conditions[1]. Production of the iron storage protein ferritin and the transferrin receptor (TfR) protein is reciprocally regulated by a translational mechanism in which the iron regulatory protein (IRP) is reversibly bound to the iron response elements (IRE) of their respective mRNAs.

A similar iron-dependent translational mechanism may be responsible for the production of divalent metal transporter I (DMTI) responsible for the uptake of ferrous iron from the brush border of duodenal enterocytes and ferroportin (IREGI) responsible for the export of ferrous iron through the basolateral membrane of the same cells. The brush border ferric reductase, converts ferric to ferrous iron for use by DMTI, and Hephaestin, a transmembrane-bound ferroxidase, converts ferrous to ferric iron, creating a concentration gradient of ferrous iron across the cell membrane facilitating iron egress. At low iron conditions the translation of TfR, DMT1 and ferroportin is enhanced, with the opposite occurring at high iron conditions.

In addition, a new protein, Hepcidin, has been described recently and is probably the most important regulator of iron homeostasis [2]. Hepcidin functions as an inhibitor of iron absorption and of release from macrophages. Its production is increased by iron overload and inflammation and is suppressed by iron deficiency. Thus, in iron deficiency powerful compensatory mechanisms involving increased activity of iron transport proteins and inhibition of Hepcidin are activated in order to restore normal iron balance. However, these mechanisms are only partly effective, and iron deficiency anemia (IDA) is one of the most common problems in clinical hematology.

Genetics of hereditary hemochromatosis

The HFE protein combines with β_2-microglobulin for presentation on the cell surface. The central role of HFE mutations in the pathogenesis of HH is clearly illustrated by the development of severe hemochromatosis in HFE knockout mice [3]. It is quite likely, that the HFE protein does not regulate directly iron absorption and relase from macrophages, but indirectly through the control of hepcidin production.

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Both hepcidin and HEF are expressed mainly in hepatic parenchymal cells. Serum hepcidin in HH is inappropriately low, and may be responsible for increased intestinal iron absorption and the lack of reticuloendothelial iron accumulation characteristic of HH. It is also quite likely that inappropriately low hepcidin production may be the final common pathway of TfR 2 (a transmembrane protein homologous with TfR) mutations and other hereditary iron overload syndromes characterized by the HH phenotype. Mutations of hepcidin, TfR 2, ferroportin, L-ferritin IRE, or atransferrinemia may all result in the hereditary hemochromatosis phenotype or inappropriately high serum ferritin. However in Western populations, HH is attributed in over 80% of subjects to homozygous C282Y mutation or compound heterozygosity for the C282Y and H63D mutations of HFE.

Transfusional siderosis

The subtle balance of normal iron homeostasis is grossly overwhelmed by the abnormal erythropoiesis associated with thalassemia major. As a result of ineffective erythropoiesis, plasma iron turnover increases 10 to 15-fold [4], resulting in the outpouring of catabolic iron which exceeds the iron-carrying capacity of transferrin. This results in the emergence of toxic non-transferrin-bound iron (NTBI) which is directly involved in the production of harmful oxygen derivatives and damage to vital tissues such as the heart, liver and endocrine organs [5]. NTBI is efficiently chelated by deferoxamine (DFO) and other iron chelators, preventing peroxidative damage and even reversing existing damage. The long-term efficacy of DFO has been extensively documented in large multicenter trials.

Iron chelation therapy

Effect of deferoxamine

The introduction of DFO for iron chelation therapy of transfusional siderosis has changed the life expectancy and life quality of patients with thalassemia major. Its long-term efficacy has been extensively documented in large multicenter trials in Italy and elsewhere.[6] In a recent report on thalassemic patients treated by DFO at a single institution, survival at 40 years was 83% and in compliant patients born after 1975 survival at 25 years was 100% [7]. The cohort-of-birth related improvement in survival was reflected in an inverse, mirror-like decrease in cardiac mortality, supporting the assumption that prevention of cardiac mortality is the most important beneficial effect of DFO therapy.

The strongest direct evidence supporting the beneficial effect of DFO on hemosiderotic heart disease is the reversal of established myocardiopathy in some far advanced cases. In former years, the course of established myocardial disease in transfusional hemosiderosis was uniformly fatal. More recent experience indicates that such patients may still be salvaged by intensified chelating treatment. Employing continuous 24-hour i.v. DFO infusion via indwelling catheters, Davis and Porter achieved reversal of cardiac arrhythmias and congestive heart failure [8]. The actuarial survival of their 17 high-risk thalassemic patients (15 with established cardiac disease) following intensification of iron chelation was 61% at 13 years and none of the compliant patients died. Reversal of cardiac arrhythmia, previously unresponsive to medical treatment was achieved in 6 of 6 patients. This occurred in some cases within a few days of starting treatment and therefore cannot be attributed to normalization of iron stores but to the depletion of a putative limited toxic labile iron pool. Miskin et al. described 8 thalassemic patients with poor compliance and symptomatic heart disease attributed to iron overload, in whom standard s.c. therapy was replaced by drug administration via an indwelling central venous line for 8–10 hours daily [9]. Following intensification of iron chelation treatment, reversal of all cardiac abnormalities has been achieved.

Unfortunately, compliance with the rigorous requirements of daily subcutaneous infusions is a serious limiting factor and in non-compliant patients life expectancy is no different from that in the pre-DFO era. This is the rationale behind the intensive efforts to identify alternative, orally effective iron chelators.

These efforts have led to the development of several important compounds including deferiprone (L1, DFP) and the bishydroxyphenyl thiazole ICL670.

Effect of deferiprone

Treatment with the oral chelator deferiprone (DFP) should be considered in patients unable to use deferoxamine or patients with an unsatisfactory response to deferoxamine as judged by liver iron and serum ferritin measurements. At a DFP dose of $75\,\mathrm{mgkg^{-1}day^{-1}}$, iron stores may decrease in some patients, remain stable in others and increase in some others [10]. Thus, careful monitoring of iron stores, preferably by measurement of tissue iron and of cardiac function is important during treatment with DFP as it is with DFO.

A few long-term, prospective trials are now available comparing the ability of chelation therapy with either deferoxamine or deferiprone to prevent heart disease In a recent study, 54 DFP-treated patients were compared with 75 DFO-treated patients retrospectively for cardiac complications and survival [11]. Although this was a non-randomized study, the age, duration of chelation therapy, mean serum ferritin

and percentage of initial cardiac dysfunction in the two groups were comparable. By the end of the 6-year follow-up period 3 patients died, all in the DFO group, despite attempted rescue by intensified i.v. therapy. Worsening of pre-existing cardiac disease or new onset of cardiac abnormalities was observed in 4% of the deferiprone group compared with 20% of the DFO-treated patients.

Anderson et al. [12] have shown significantly higher T2* values, presumed to reflect lower cardiac iron concentrations in patients treated long term with DFP than in patients treated with DFO. The authors concluded that conventional treatment with DFO did not prevent excess cardiac iron accumulation in more than half the patients with thalassaemia major and that oral DFP was more effective at removing cardiac iron. This was a retrospective non-randomized study and, although great efforts were made for proper matching of the two groups, only 15 patients were treated by DFP whereas the 30 DFO controls had to be selected from a large group of 160 patients receiving DFO. The important points raised by this report should be further studied by prospective randomized trials involving sufficient numbers of patients.

Effect of ICL670

ICL670 is a new once-daily tridentate oral chelator requiring two molecules to form a stable complex with each iron atom. ICL670 promotes iron excretion mainly in the bile [13]. A large international, multi-center trial has been conducted in 586 thalassemic patients randomized to receive ICL670 once daily at doses of 5, 10, 20 or 30 mgkg^{-1}, or subcutaneous DFO at doses of 20–60 mgkg^{-1}day^{-1} for 5 days/week. The effect of ICL670 on liver iron concentration was dose-dependent. Doses of 20 and 30 mg /kg induced stable or falling liver iron concentrations whereas doses of 5 and 10 mgkg^{-1} were too low to induce a negative iron balance. ICL670 was generally well tolerated. These data indicate that ICL670 is well-tolerated, and effective by once-daily oral administration for the treatment of chronic iron overload in beta thalassemia patients receiving regular blood transfusions [14].

Combined chelation

Improved chelating efficiency and improved compliance with combined deferiprone and DFO regimen has been first reported by Wonke et al. [15] in thalassemic patients. Deferiprone was given daily, and DFO 5 days per week. This has resulted in a decrease in serum ferritin in all 13 patients previously failing to respond to standard deferiprone treatment. The effect of combined DFO and DFP on UIE

appeared to be additive, and no toxic side-effects have been observed. Combined therapy reduces serum ferritin in patients who had previously failed to achieve a satisfactory response to DFP alone. This approach to chelation therapy may be an attractive option for patients who are unable to comply with DFO infusions on more than a few days a week and who have an inadequate reduction of iron stores with DFP alone. To date, this combination therapy has shown no unanticipated side effects when given for periods of a year or more.

It is to be hoped, that better understanding of the pathophysiology of iron toxicity and the mechanism of iron chelation may promote the development of improved strategies of iron chelation therapy.

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