

Iron Chelation Basics

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With iron chelation therapy, a chelating drug binds with free or “labile” iron in the blood and organs, which allows for removal of excess iron from the body. When multiple transfusions are repeatedly needed and phlebotomy is not possible, chelation therapy provides a means of controlling iron overload.

The goals of iron chelation therapy are two-fold. The first goal is to maintain iron balance by keeping body iron at safe levels. Once storage iron has accumulated, the process of restoring safe levels is slow because storage iron is not directly chelatable and in some tissues, such as the pituitary, damage from storage iron may never be reversed. Therefore, prevention of iron accumulation is more desirable than rescue therapy. Secondly, chelation should detoxify labile iron pools in plasma and in cells, even at times when storage iron is at high levels. Provided they can be accessed by the chelator, labile iron pools are more available for rapid chelation than storage iron pools. Because labile iron pools are rapidly turned over, 24-hour chelation is desirable to minimize damage from intracellular or plasma labile iron species. In iron overload, iron is continuously delivered to tissues possessing the relevant receptors through plasma non-transferrin-bound iron (NTBI) and thus effective chelation should continuously chelate plasma NTBI species. The ideal chelator accomplishes these goals while still providing an acceptable chelator toxicity/efficacy profile. In practical terms, the monitoring of the ideal chelator should be simple and with few obstacles to patient compliance.

Chelators may be categorized by their binding structures. Deferiprone (DFP) is a bidentate chelator requiring three molecules each with two iron binding sites for the six coordination sites of iron(III). Deferasirox (DFS), a tridentate chelator, requires two molecules for iron(III) coordination, and desferrioxamine (DFO) is a hexadentate chelator binding iron in a 1:1 ratio. In general, hexadentate chelators form the most stable iron-chelate complexes and bidentate chelators the least stable.

Long recognized as the first-line treatment in iron overload, desferrioxamine has been used in patients with iron overload since the early 1960s, although current infusion regimens were only introduced in the late 1970s. Survival and complications from iron overload have steadily improved in cohorts of thalassaemia major patients born since this time. DFO effectively reverses iron-mediated heart failure but removes heart storage iron (as measured by T2*) relatively slowly, particularly when given at low doses and intermittently. The drug is not effectively absorbed from the gut and has a short plasma half-life, so optimal therapy is achieved only by continuous infusion by the subcutaneous or intravenous routes. These are not convenient regimens, and poor compliance with DFO has been a limiting factor in effective treatment for many patients. At conventional doses, DFO is well tolerated, but excess doses relative to the degree of iron overload can give rise to unwanted effects, including retinopathy, ototoxicity, and growth retardation.

Deferiprone has been registered outside North America since the late 1990s as second-line treatment in patients with thalassaemia major when desferrioxamine therapy is contraindicated or inadequate. Deferiprone's advantages are convenience of oral therapy and an ability to decrease cardiac iron. Deferiprone may be less effective than desferrioxamine in controlling total body iron overload, as measured by liver iron concentration. Deferiprone has a short plasma half-life, requiring 3x-daily oral dosing without chelation cover at night; this regimen may also impact patient compliance. Its adverse event profile is also less than ideal and includes neutropaenia, agranulocytosis, and arthralgia. The relationship of dose or iron loading to these effects has not been clearly established.

By alternating desferrioxamine at night with deferiprone 3x/day, 24-hour chelation may be achieved, thereby decreasing labile plasma iron species over 24 hours and better controlling body iron levels. Other combination regimens of desferrioxamine with deferiprone may not provide 24-hour protection, but improvements in cardiac T2*, ferritin levels, and left ventricular function have been demonstrated.

Deferasirox is a high-specificity iron chelator that provides 24-hour coverage in a once-daily oral dose. Because of its long half-life, it does not require continuous dosing in order to remain effective. Deferasirox produces dose-dependent reductions in body iron levels, as estimated by liver iron concentration and/or serum ferritin. Not all patients on deferasirox achieve negative iron balance at the current highest recommended dose of 30 mg/kg/day. The dose required is influenced by the rate of transfusional iron loading. Effectiveness and tolerability have been evaluated in prospective studies across a range of transfusion-dependent anaemias, including thalassaemia major, sickle cell disease, myelodysplasia, and rarer anaemias, such as Diamond Blackfan anaemia. Although deferasirox is generally well tolerated, unwanted effects include gastrointestinal upset, skin rash, and increases in serum creatinine in about a third of patients. These are non-progressive and can be managed where necessary by dose modification. Data on cardiac effects from deferasirox are currently limited, and the follow-up period of long-term studies for deferasirox is < 5 years.

Suggested Readings

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