Role of Iron Chelation Therapy in Thalassemia Major

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In chronic anemias associated with iron overload, iron chelating therapy is the only method available for preventing early death caused mainly by myocardial and hepatic iron toxicity. Although desferrioxamine (DFO) has been available for treating transfusional iron overload from the early 1960s, the era of modern and effective iron chelating therapy started only 20 years ago with the introduction of subcutaneous DFO infusions by portable pumps. Today, long-term DFO therapy is an integral part of the management of thalassemia and other transfusion-dependent anemias, with a major impact on well-being and survival[1,2].

DESFERRIOXAMINE (DFO)

The effect of DFO treatment, measured by urinary iron excretion, is directly proportional to the severity of iron overload. Hence, treatment in subjects without iron overload will result in limited iron excretion. However, treatment should not be introduced too late if the objective is the prevention of iron toxicity. It should be started when serum ferritin levels reach about 1000 µg/L which usually occurs after the first 10 or 20 transfusions[3]. DFO is infused via thin s.c. needle inserted to the arm or abdomen nightly, connected to a portable pump over 8-12 h, 5 to 7 times per week at a daily dose of 20 to 40 mg/kg. A urinary iron excretion of 0.5 mg/kg/d is usually sufficient to ensure negative iron balance.

Although prolonged subcutaneous DFO infusion is universally recognized as the optimal method of treatment, twice daily s.c. injections may yield similar amounts of urinary iron[4]. A new delivery system for continuous DFO infusion has been introduced by Baxter allowing continuous 48 h s.c. or continuous 24 h IV delivery for 7 days each week[5]. This technology allows effective removal of toxic free iron (NTPI) from the plasma, a significant decrease in serum ferritin within 4 weeks, and improves patient compliance compared to conventional s.c. DFO pumps. Compliance with the new disposable Baxter device allowing continuous DFO delivery for 48 or 120 hours in a group of 26 thalassemic patients from Turkey has been quite satisfactory[6].

Response to treatment may be assessed by serum ferritin measurements, liver biopsies, computed tomography, or magnetic susceptibility (SQUID)[7]. Quantification of liver iron concentration with magnetic resonance imaging by combining T1-, T2-weighted spin echo sequences and a gradient echo sequence is an improved noninvasive method allowing liver iron measurements ranging from low normal up to 150 mmols/kg dry weight[8]. The use of MRI for iron measurements in other organs is less reliable and no cor-

relation has been found between pituitary MRI measurements, the GnRH stimulation test and the clinical status of thalassaemic patients[9]. The assessment of serum non-transferrin iron (NTBI) may contribute to the documentation of chelatable iron depletion during treatment[10]. The presence of NTBI in most patients with thalassemia major and it rapid disappearance on starting DFO infusion emphasises the nees for continuous DFO in high risk patients[11]. Serum ferritins are disproportionately low in patients with coexistent ascorbate deficiency and high in active liver disease or inflammation[12]. Nevertheless, serum ferritin is the most accessible and inexpensive tool for the long-term monitoring of chelating efficiency. It has been suggested that protection from cardiac complications may be achieved when ferritin levels are kept below 2.500 µg/L but others have suggested a serum ferritin below 1000 µg/L or below 1500 µgLl is needed[13,14,20]. A recent study has suggested that the combination of liver iron < 7 mg/g dry weight and serum ferritin < 1500 µg/L is needed to predict for survival free of cardiac disease.

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. Earlier experience in hereditary hemochromatosis has shown that the myocardiopathy of iron overload is potentially curable by effective iron mobilization through phlebotomy. However, in transfusional hemosiderosis, the course of established myocardial disease was uniformly fatal and, until recently, believed to be nonresponsive to iron chelating therapy. Several reports indicate that such patients may still be responsive to aggressive chelating treatment. Marcus et al described first the reversal of established symptomatic myocardial disease in 3 of 5 patients by continuous high-dose (85-200 mg/kg/d) IV DFO therapy at the cost of severe reversible retinal toxicity[15]. Reversal of symptomatic myocardiopathy has been reported by others, without significant drug toxicity[16]. Continuous 24-hour ambulatory intravenous infusion of DFO through central venous ports, using standard portable infusion pumps or the new Baxter delivery system is a very effective method for the rapid reversal of established hemosiderotic heart disease[5]. In addition, it is an excellent tool for improving patient compliance allowing uninterrupted delivery of DFO and the effective depletion of very large iron stores.

DEFERIPRONE (L1)

In spite of the proven efficacy of DFO, not all patients are willing to cope with the rigorous requirements of the long-term use of portable pumps. In addition, the high cost of this treatment is a serious obstacle to its more widespread use. In view of these considerations, there is a great need for the development of alternative, orally effective iron chelating drugs. Within recent years more than one thousand candidate compounds have been screened in animal models. These efforts have led to the identification of several interesting compounds, a few of which may be of possible clinical usefulness. The present discussion will be limited to the most outstanding of these compounds including deferiprone (L1); pyridoxal isonicotinoyl hydrazone (PIH); the polyanionic amines; the substituted polyaza compounds, and; bishydroxyphenyl thiazole[17-20]. Of all the new iron chelating drugs available today, only deferiprone has been used as a substitute for DFO in clinical trials involving many hundreds of patients. The pharmacology and clinical efficacy of L1 has been the subject of several reviews[21-23].

Initial clinical studies showed that the drug was capable of causing urine excretion equivalent to that with a similar dose of DFO[24]. Side effects noted in early studies included agranulocytosis, arthropathy and gastrointestinal toxicity[25,26]. In contrast to DFO, side effects with L1 occurred in patients with high iron burdens. The results of long-term iron chelating therapy with L1 in thalassemic patients in London, Toronto, Bern and Bombay have been summarized in several reviews and the combined experience of the 4 major European and Canadian groups pioneering the clinical use of L1 has been described in a report of the International Study Group for Oral Iron Chelators (ISGOIC) [21-23,27-31]. Subsequent experience in thalassemic patients on long-term L1 treatment has been reported by Olivieri et al, Hoffbrand et al and Tondury et al as well as a major multicenter study empoying the Apotex formulation of L1, involving 187 patients from Cagliari, Torino, Ferrara, Philadelphia and Toronto (the LA-02 study)[32-35]. All patients received a daily L1 dose of 75 mg/kg. By comparison with the ISGOIC study summarizing L1 experience prior to June 1994, these recent reports indicate a higher rate of treatment discontinuation (39 vs 20%), failure to decrease serum ferritin and liver iron concentrations to levels assuring significant cardioprotection in a substantial proportion of cases and in-

deed, the continued presence of cardiac mortality, a complication of transfusional iron overload which has already been largely eliminated by effective DFO treatment. A recent meta-analysis of nine clinical trials providing data on 129 iron overloaded patients, has shown that after a mean of 16 months, 75% of patients with severe iron-overload had a decrease in serum ferritin as compared with baseline, and 52% achieved a negative iron balance[36]. Other reports from Mediterranean and Near-Eastern countries describe a high compliance rate in patients not previously compliant with DFO treatment, good tolerability and a significant decrease in serum ferritin within the first year of L1 treatment[37,38].

The failure to achieve a steady decrease in storage iron with L1 is explained by the difference in efficacy between the two drugs on a weight per weight basis. As shown by a metabolic balance study comparing combined urinary and fecal iron excretion in thalassemic patients receiving either 60-mg/kg DFO or 75 mg/kg PO L1, mean iron excretion on L1 was only 65% of that on DFO[39]. However, in some patients L1 was as or more effective, than DFO.

COMBINED CHELATION THERAPY

In patients with unsatisfactory response to deferiprone, a number of options are available. The dose of L1 may be increased from the standard 75 mg/kg/d to 100 mg/kg/d[40]. Alternatively, L1 given daily, may be combined with DFO on 1-7 days per week. Such measures resulted in a decrease in serum ferritin in all patients previously failing to respond to standard L1 treatment[40]. The effect of combined DFO and deferiprone on urinary iron excretion appeared to be additive, and no toxic side-effects have been observed over several years of combined therapy (Wonke & Hoffbrand unpublished). Metabolic studies confirm that combined therapy is at least as effective as the drugs given sequentially at increasing urinary and faecal iron excretion. Improved results have also been reported following alternate use of deferiprone and DFO which may be due to improved compliance[41].

The combination of a weak chelator which has a better ability to penetrate cells, with a stronger chelator that penetrates cells poorly but has a more efficient urinary excretion, may result in a synergistic effect through iron shuttling between the two compounds. Such a “shuttle” effect was first proposed by Grady. Metabolic balance studies performed by Grady et al in thalassemic patients have shown, that when deferiprone is given during DFO treatment (at time 0.4 and 8 of an 8-hour infusion), a synergistic effect is achieved, with total iron excretion 2.4 to 3.4 times higher than with DFO alone[42]. These data suggest an interaction between deferiprone and DFO, and may have important implications to the design of new strategies in iron chelating treatment.

A shuttle effect was directly demonstrated by following the fate of chelated plasma iron in thalassemic patients receiving combined DFO and L1 therapy[43]. L1 treatment resulted in the temporary accumulation of chelated iron in the plasma peaking at 2 hours. The addition of DFO to L1 treatment resulted in the transfer of chelated iron from L1 to DFO and an increase in total chelated iron in the serum. This chain of events indicates improved in vivo chelating efficiency utilizing chelatable iron first mobilized by L1, and transferred subsequently to DFO.

Combination treatment using a lowered dose of L1 (50 mg/kg/d) daily and DFO by subcutaneous infusion 50 mg/kg/d twice weekly in 28 patients resulted in a marked decrease in the incidence of GI symptoms and arthropathy and a decrease of serum ferritin from 3724 to 1790 within 16 ± 9 months[44]. Others have reported improved compliance when DFO was given over the weekend for 2 days, alternating with L1 for 4 days per week, although the 6 month study period did not allow firm conclusions regarding cumulative efficacy[41].

Iron chelating therapy has changed the quality of life and life expectancy of thalassemic patients. However, the high cost and rigorous requirements of DFO therapy, and the significant toxicity of deferiprone underline the need for the continued development of new and improved orally effective iron chelators. Such development, and the evolution of improved strategies of iron chelating therapy require better understanding of the pathophysiology of iron toxicity and the mechanism of action of iron chelating drugs.

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