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Oral iron chelation therapy with deferiprone in patients with iron overload

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Despite the introduction of parenteral iron chelation with desferrioxamine over thirty years ago, 50% of patients with thalassemia major die before the age of 35, mostly due to heart failure secondary to iron overload. Although desferrioxamine can reduce or stabilize iron load, many patients do not receive adequate therapy with this chelator, mainly due to intolerance to a regimen that requires parenteral administration for an extended period of time, five to seven days per week. For these patients, deferiprone, an orally active chelator, is a treatment alternative to control iron overload. The safety and efficacy of deferiprone have been demonstrated in a large number of clinical trials. It is estimated that over six thousands patients with iron overload have already been treated with this chelator, and some of them have been taking the drug for over 10 years. Deferiprone-induced iron excretion is directly affected by the dose of deferiprone and the patient's iron overload. Recently, it has been demonstrated that desferrioxamine and deferiprone have different chelating capabilities and that their concomitant or sequential use promote an additive or synergistic iron excretion with a rapid reduction in the body's iron load. It is now possible to consider tailor-made chelation regimens based on individual patient needs. Rev. bras. hematol. hemoter. [Brazilian Journal of Hematology and Hemotherapy] 2003;25(3):177-188.

Key words: Deferiprone; desferrioxamine; thalassemia; chelation.

Introduction

Iron chelation therapy is essential for the survival of patients with hemosiderosis secondary to red blood cell transfusions.[1-3] Until recently, only one iron chelator, desferrioxamine (DFO) was available for the clinical treatment of these patients.

However, many patients do not tolerate the subcutaneous and intravenous infusions of DFO, for

The efficacy and safety of the use of DFO, as well as its efficacy in increasing the survival of patients with iron overload, have been well documented in the last two decades.[4-6]

Clinical studies have shown that the fecal excretion of iron corresponds to an average of 20% of the total

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8 to 12 hours for at least five days per week.[7-9] Additionally, in many patients, DFO causes irritation in the infusion site, and as well as bone abnormalities and stunted growth, in addition to neurotoxic, visual and hearing [adverse] effects.[7-9] Intolerance to chelation therapy is considered to be the main cause of death in patients with iron overload, especially in patients with thalassemia major.[1,6,7,10] In the last few decades an intense search for less aggressive[11-13] chelation therapies and for oral chelators has been in progress. Hundreds of chelators were developed, but only deferiprone demonstrated acceptable results for its use in clinical practice.

Deferiprone (1.2 dimethyl-3-hydroxypyrid-4-one, L1) is a synthetic chelator developed at King's College of London in 1984. It is estimated that over six thousand patients with iron overload, most of them with thalassemia, have already received treatment with deferiprone and some patients have been taking the drug for ten years or more.[10,15-25] This article is a review of recent clinical studies conducted with deferiprone and of its new potential use in clinical practice.

Pharmacokinetics

Deferiprone is an orally active iron chelation agent that preferentially chelates the trivalent iron cation (Fe3+) creating a deferiprone/iron complex in a molar ratio of 3:1 (3 deferiprone: 1 iron), which is excreted together with the free drug. Studies conducted in animals have demonstrated that 92% to 99% of the dose of deferiprone administered orally is rapidly absorbed by the gastrointestinal tract.[26] These findings were confirmed in patients with thalassemia major where the peak plasma concentration of the drug was reached within 45 to 60 minutes after ingestion and over 90% of the dose was eliminated as free drug within five to six hours after its administration.[27-29] The concomitant ingestion of food reduces the absorption speed but does not reduce the amount of absorbed drug.[30-31] In patients with iron overload, approximately 85% of the dose of deferiprone ingested is metabolized in an inactive glucuronide conjugate, which is excreted in urine together with the deferiprone: iron complexes.[28-29] eliminated, varying from 0% to 60% in some patients.[32-34]

Efficacy

The efficacy of deferiprone has been evaluated in patients with secondary hemosiderosis, especially in those with thalassemia major, due to its capacity to boost iron excretion, its effect on the levels of serum ferritin and on iron overload in the liver and heart.

Iron excretion

Clinical studies have demonstrated the efficacy of deferiprone in inducing the excretion of iron in patients with hemosiderosis.[15-17,35-37] The amount of iron eliminated is, generally, directly influenced by the dose of deferiprone and by the patient's iron overload level.[15,36-39] Metabolic studies of iron balance have shown that 25 mg of deferiprone, three times a day, causes iron excretion similar to the excretion caused by 40 mg of desferrioxamine.[22,37,41,43-45] This dosage causes an iron excretion that neutralizes the iron introduced by transfusions in most patients undergoing chronic transfusion regimens. Iron urine excretion in response to the use of deferiprone is not affected by the concomitant administration of vitamin C or food.[15,27]

Serum ferritin

New procedures, such as magnetic resonance imaging (MRI) and magnetic susceptometry (SQUID) have been developed for the evaluation of iron concentration in several organs. However, the measurement of serum ferritin continues to be the most commonly used diagnostic method in clinical practice for the assessment of iron overload. Due to the variability of its results, a single measurement of serum ferritin has limited diagnostic value in the assessment of the efficacy of a chelation therapy.[46] However, serial measurements of ferritin generally reflect the changes in liver iron concentration and provide a relatively precise indication of the efficacy of the chelation therapy, indicating if the iron overload is static, increased or decreased.[40-42] Moreover, serum ferritin level continues to be considered the most important prognostic factor in patients with iron overload.[43,44]

Clinical studies with deferiprone have demonstrated that its use decreases or stabilizes serum ferritin levels in patients undergoing chronic transfusion treatment regimens (Figure 1).[42,45-47] Comparative studies have shown that deferiprone has an efficacy similar to that of DFO.[42,48] Similarly to what is found with DFO,[49] the intensity of the response to deferiprone is directly proportional to the dose used and to the level of iron overload at the beginning of the treatment. Patients with a higher level of iron overload at the beginning of the treatment have the highest decrease during treatment with deferiprone, while patients with a lower level of iron overload at the beginning of the treatment have steady or slightly increased levels of serum ferritin.[16,45-47] While studying 532 patients who were taking deferiprone, Ceci et al. found that patients who started treatment with serum ferritin levels >4,000 mg/L had a significant and steady decrease in serum ferritin, while patients who started treatment with ferritin levels <2,000 mg/L did not present with significant changes.[47] Moreover, Wonke et al. have demonstrated in a study with nine patients considered to be inadequately chelated at a dose of 75mg/kg/day of deferiprone that a slight increase in the dose, to 83–100 mg/kg/day, or its combination with DFO, produced a significant decrease in ferritin level and in liver iron concentration within a few months of treatment and without any new side-effects.[50]

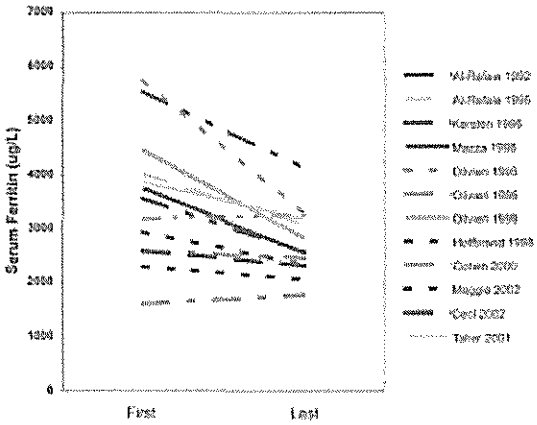

Fig.1 - Serum ferritin levels in patients undergoing chronic transfusion treatment regimen treated with deferiprone. Each line represents the mean iron ferritin level at the beginning and at the end of treatment with deferiprone in patients participating in each of the studies above.

Liver iron concentration

The determination of liver iron concentration (LIC) has the advantage of measuring the amount of iron in the organ that presents the highest overload of this mineral, and its concentration provides a relatively precise estimate of the total level of iron in the body.[51] LIC can be determined by biochemical measurement of liver fragments obtained through biopsies or through magnetic biosusceptometry (SQUID). However due to the inconvenience of repeated liver biopsies and the limited availability of SQUID (only four machines, two in the USA and two in Europe, are currently active in clinical use), only a few studies have used sequential LIC determination to evaluate the effect of chelation therapy with desferrioxamine or with deferiprone. Moreover, when LIC is evaluated in biopsy fragments, it can present a large variability, which can make it difficult to interpret the chelation effects in some patients. This variability can be explained by factors such as inadequate size of the samples obtained through the biopsies and heterogeneous distribution of iron in the liver parenchyma, especially in the presence of severe fibrosis or cirrhosis.[52-55] Recently, there have been attempts to evaluate LIC through magnetic resonance imaging (MRI).

The studies that evaluated LIC during treatment with deferiprone have produced results similar to those of serum ferritin, with its decrease or stabilization, despite continuous transfusion-induced iron overload (Table 1).[24,41,42,56,57] In one of the studies, the authors compared the efficacy of deferiprone and of DFO on LIC alterations, evaluated through liver biopsies, in patients with thalassemia major.[42] The authors have shown that deferiprone and DFO were equally effective in decreasing liver iron concentration.

Heart iron concentration

Since heart disease is responsible for most of the deaths of patients with thalassemia major (78%) a decrease in heart iron load is the most important element of a chelation therapy.[58]

Several magnetic resonance methods have been used to evaluate heart iron load. These studies demonstrate that deferiprone is as effective as, or superior to, DFO in the clearance of heart iron, as shown in the studies on table 2. Maggio et al. have compared heart iron concentration using MRI in 145 patients treated with deferiprone or DFO.[42] After one year of the study, the use of both chelators produced a similar increase in the intensity of the magnetic resonance signal, compatible with a decrease in heart iron. Studies conducted for longer periods and with magnetic resonance techniques that are considered to be more precise have shown a higher efficacy of deferiprone in the removal of heart iron than the use of subcutaneous DFO. Another randomized study, which evaluated patients treated with deferiprone for an average period of 22 months, has shown a significant improvement in T2 relaxation time, compatible with a reduction in heart iron, in patients treated with deferiprone (initial T2 = 23.9±6.4 ms; final = 32.4±9.3 ms; p <0.0005), which remained unaltered in patients treated with DFO (initial = 21.4±7.9; final = 21.7± 6.9 ms; p >0.67).[59] In an evaluation of another group of patients receiving deferiprone for a longer period (2.9±1.3 years), the same authors have also found a significant improvement in heart T2 relaxation time (initial T2 = 26.6±8.4 ms; final = 30.5±6.7 ms; p <0.005).[60]

More recently, a study has demonstrated that the evaluation of T2* (T2-star) is a promising method for the early diagnosis of myocardial iron overload. The authors evaluated heart iron concentration and heart function in patients treated for at least three years with deferiprone or DFO. Deferiprone was not only more effective than DFO in the removal of heart iron but also in the improvement of heart function.[61] Pennel & Bland demonstrated that T2* has a better predictive effect of ventricular dysfunction than serum ferritin or liver iron concentration.[62]

Another indication of the higher efficacy of deferiprone in relation to DFO in the reduction of heart iron was demonstrated in a retrospective study that compared the occurrence of cardiomyopathy and survival in patients with thalassemia major treated with deferiprone or DFO, for a minimum period of four years in a single treatment site. At the end of the study period, the rate of cardiomyopathy in patients treated with deferiprone was four times lower than in patients treated with DFO (p = 0.007). The three patients who died due to heart failure during the study period had been treated only with DFO.[63]

The mechanism of the apparently better cardioprotective effect of deferiprone can be attributed to its higher lipophilicity and lower molecular weight than DFO, which facilitates its transit through the cell membrane and a more effective chelation of the intracellular iron.[64]

Despite the fact that the global data currently available demonstrates that the efficacy of deferiprone is comparable, if not superior, to that of DFO in the elimination of heart iron, the efficacy of deferiprone in patients with heart failure secondary to iron overload is not yet known.

Table 1
Mean liver iron concentration at the beginning and at the end of chelation therapy with deferiprone in patients undergoing chronic transfusion treatment regimen

Author	Measurement Method	No. of patients	Dose (mg/kg/day)	Duration (years)	Liver iron	
					Initial	Final
Mazza et al [22]	Biopsy	20	70	>1	16.2 mg/g	21.0 mg
Olivieri et al [20]	SQUID or biopsy	21	75	3.1	80.7 µmol/g	46.8 µmol/g
Olivieri et al [45]	SQUID or biopsy	18	75	4.6	88.7 µmol/g	65.5 µmol/g
	NMR	71	75	1.0	0.83 [ISR]	0.89 [ISR]
Maggio et al [42]	Biopsy	20	75	2.5	4.4 mg/g	2.3 mg/g

SQUIB [*sic*: SQUID] = **Superconducting Quantum Interference Device Biosusceptometer**

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