Haematologica 2000; 85:115-117
original paper

Red Cells & Iron

Chelation therapy in patients with thalassemia using the orally active iron chelator deferiprone (L1)

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ABSTRACT

***Background and Objectives*. Excessive hemosiderosis is the main reason for the multi-organ failure observed in multitransfused patients. Deferiprone (1,2-dimethyl-3-hydroxy-pyridine-4-one, L1) is an orally active iron chelator mainly excreted via urine. We conducted a study in order to determine the efficacy and safety of L1 in Greek thalassemic patients.**

***Design and Methods*. A group of 11 thalassaemic patients entered the study; L1, the Cipla formulation for deferiprone, at a daily dose of 75-100 mg/kg bw t.i.d. was used. After giving informed consent all patients were subjected to clinical examination and biological tests.**

***Results.* All patients tolerated the L1 well; there were no significant side effects (except for slight gastrointestinal disturbances for the first days). The net urinary iron excretion ranged from 6.96 to 26.1 mg/24h. Serum ferritin declined within 4-6 months in most of the patients.**

***Interpretation and Conclusions.* The results suggest that L1 is a rather safe drug which decreases iron overload without causing any considerable side-effects in Greek thalassemics.**

Key words: thalassemia, transfusion, iron, deferiprone

Removal of iron excess is the mainstay of the treatment of iron overload caused by multiple transfusions for thalassemia syndromes. Regular subcutaneous administration of deferoxamine (DFO) has dramatically altered the prognosis of thalassemia major and is considered the standard iron cheating-therapy at present.[1] Unfortunately DFO must be given parenterally and is expensive, making it unavailable for long-term use in many parts of the world. Poor compliance with DFO is a frequent problem in thalassemic patients, while allergy to this drug is less commonly observed. Deferiprone (L1) is an orally active iron chelator that has been shown to reduce body iron to concentrations compatible with the avoidance of complications from iron overload in patients with thalassemia and related disorders.[2,3] Deferiprone binds iron in a 3:1 ratio at pH 7.4.[3,4] The drug permeates cell membranes because of its neutral charge and forms neutral iron complexes, so it can remove iron from iron-storage proteins, ferritin and hemosiderin.[4,5] Because of equilibrium between various iron pools, excess iron stored in organs is also mobilized.[2,4,5] The quantification of iron urinary excretion appears to be a reliable indicator of the overall elimination of body iron.[3,5]

Deferiprone is rapidly absorbed and appears in the blood within minutes.[6] Maximum serum concentrations were observed within 12 minutes to 2 hours after oral intake.[3] The quantity of iron excreted by deferiprone is related to three main factors: a) dose, b) frequency of administration and c) iron load of the patient. In general, the higher these factors, the more iron is excreted.[2] Variations between patients in relation to rates of absorption, metabolism and clearance have been observed. Deferiprone seems to be highly selective for iron, a fact that leads to no considerable excretion of most biologically important trace elements namely: calcium, magnesium, copper, aluminium.[6]

The adverse effects observed during international studies for periods of up to 4 years have been musculoskeletal pain and arthralgia (35%), gastric intolerance (20%), agranulocytosis (1-2%) and zinc deficiency (1%). Withdrawal of therapy led to resolution of these symptoms.[2,4,5]

The first trials in humans began in the U.K. in 1987. Trials have been conducted in Canada, the Netherlands, Italy, Germany, India, Switzerland, Russia, Czechoslovakia, Belgium, Sweden, Greece, Norway, USA, and Cyprus.[2,4] We conducted a study in order to determine the efficacy and safety of L1 in Greek thalassemic patients.

Design and Methods

A total of 11 patients entered the protocol. We used the Cipla formulation of L1 (tablets 500 mg). The trial inclusion and exclusion criteria are listed in Table 1. Four of our subjects (cases #1, 2, 3, 4) had used DFO before entering the protocol; the remaining 7 were not using DFO because of allergy.

Schedule of the protocol

- Informed consent, personal data, medical history, clinical examination, previous/current therapy:

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at the first visit to the hematologic center.
- Hemoglobin electrophoresis, DNA, HLA, hepatitis B virus markers, HCV, HIV, investigation for blood coagulation, lymphocyte subpopulations: at the first visit to the clinic.
- Weight, performance status: weekly.
- Vital signs: weekly.
- Laboratory examination: hematologic tests, weekly.
- Laboratory examination: biochemical tests and urinalysis: at two week intervals.
- Ear, nose, throat and eye examination: monthly.
- Immunologic tests, serum iron and ferritin levels, 24-hour urine collection for iron concentration, HbsAg, HCV, HIV, ECG: every three months.
- Chest X-ray, echocardiography, radioisotopic ventriculography, serum level of Mg, Zn, Cu: every six months.

Efficacy evaluation

1. Serial serum ferritin measurements on commencement of the protocol and on completion on first and second years of administration.
2. Serial urine excretion on commencement of the protocol (with or without DFO administration) and on completion of the first and second years of administration. For the determination of urinary iron excretion, the 3307 Iron Mercotest kit after deproteinization was applied (Merc, Germany).

Results

Treatment outcome was assessed by sequential evaluation of urinary iron excretion and serum ferritin concentration. The net urinary iron excretion ranged from 10.42 to 68.55 mg/24h following L1. Iron excretion also ranged from 6.96 to 26.1 mg/24h in those receiving DFO; without any chelator it ranged from 1.39 to 3.72 mg/24h.

Serum ferritin started dropping within the first 4-6

Table 1. Inclusion and exclusion criteria for our L1 protocol.

Inclusion criteria	*Exclusion criteria*
Written voluntary informed consent given by the patient after review of the purpose, benefits and risks of the study, (complying with the requirements of the Helsinki declaration).	Chronic hepatitis with evidence of severe liver dysfunction (liver enzymes higher than 4 times upper normal limits).
Patients over 18 years old, male and female.	HIV antibody positivity.
Patients with β-thalassemia with iron overload (serum ferritin level over 2,000 ng/dL), receiving frequent erythrocyte transfusions or not.	Severe eye abnormality.
Karnofsky performance status over or equal to 80%.	Clinical evidence of overt heart disease or arhythmia.
Absolute neutrophil count over 1.8×10^9/L.	Severe hearing or visual loss.
Platelet count of 150×10^9/L.	Women during pregnancy, lactation or with child-bearing potential unless using effective contraception.
Normal biochemical parameters. (see text)	Diabetes.
Normal immunologic parameters	Evidence of autoimmune or inflammatory disease such as rheumatoid arthritis, systemic lupus erythematosus or other collagen disorders.
Evidence of acceptable cardiac function as determined by echocardiography.	Evidence of disease at time of enrollment.
Evidence of acceptable liver function as determined by SGPT, SGOT, billirubin, total protein and prothrombin time values.	

Table 2. Follow-up of iron status in the patients treated with L1.

Pat./m	*Thal.type*	*Fe input g/y*	*Ferritin 0*	*Ferritin 1st y**	*Ferritin 2nd y**	*Fe output (mg/d) no medication*	*Fe output (mg/d) DFO*	*Fe output (mg/d) L1*
1/26	major	9	5.500	5.369	3.900	0.66	14.41	22.33
2/27	major	9	2.812	4.124	4.851	3.78	15.79	50
3/9	IM	1.85	2.000	645	Stop	2.41	26.1	31.43
4/22	major	6.76	6.156	5.462	NA	2.25	6.96	68.55
5/2	IM	0.37	2.800	2.100	Stop	3.72	NA	26.9
6/24	major	9	6.500	5.022	5.013	1.89	NA	10.42
7/24	major	9	5.532	4.082	3.539	1.39	NA	18.19
8/15	major	6.76	4.999	4.960	NA	2.43	NA	23.7
9/11	IM	0.37	3.918	2.258	NA	2.21	NA	31.2
10/4	major	9	5.840	4.010	Stop	3.22	NA	25.12
11/10	major	4.5	6.000	4.307	NA	2.86	NA	25.9

*Pat./m: patients/months of observation; Thal. type: thalassemia type; IM: thalassemia intermedia; major: thalassemia major; Fe input: transfusion iron overload; *Mean values for a series of measurements for our patients (from 15 to 4), conducted on a minimum basis of 3-monthly intervals; NA: non available.*

months following commencement of the protocol. By the end of 6 months the decline was significant in all patients, except case #2, who suffered from hepatitis C infection (Table 2). One patient (case #3) stopped the drug because serum ferritin level dropped from 2,200 µg/dL to 392.4 µg/dL within 7 months.[2] Two more cases (#5 and #10) dropped out of the protocol for emotional reasons.

The quality of life perceived by patients maintained on the L1 regime was substantially improved compared to that of the DFO regime, according to their own estimation.

As previous studies have shown, a daily dose of 75 mg/kg bw of deferiprone is not always adequate to achieve negative iron balance; we increased the daily dose to 100 mg/kg/day, t.i.d. in those patients who did not achieve a negative iron balance (#1, 2, 4, 6, 8). Following this dose increase, urinary iron excretion also increased (from 0.254 to 0.353 mg/kg bw/24h. The overall compliance was considered as *excellent* in 7, *intermediate* in 3 and *poor* in 1 of the patients given the difficulties of continuous monitoring; the large number of tablets was a main factor limiting compliance. Complications of treatment and adherence to L1 therapy were assessed as well. It is of interest that the side effects encountered with L1 in our group were limited, all subjects tolerating the L1 well, experiencing only slight gastrointestinal disturbances for the first days. After twenty-four months of treatment, no significant changes were noted in the hematologic, biochemical and immunologic parameters (data not shown). No important changes in trace elements were noted (data not shown).

Discussion

This small study confirms that deferiprone can be safely used in treatment of iron-loaded patients who are not compliant with or allergic to desferrioxamine. Adverse side-effects, principally agranulocytosis and arthropathy, were not observed in our trial. However, deferiprone must still be considered an experimental drug and should be used offered only to patients who participate in clinical trials. It is worth noting that transfusion associated iron load per year in each case is highly heterogeneous (ranging from 0.37 up to 9.0 g); this explains to some extent the relatively weak response to treatment (reflected by the *resistance* of serum ferritin values). The putative role of other factors determining the severity of siderosis remains to be elucidated.[8] However, we emphasize the considerable difference in urinary excretion following L1 administration regardless of iron loading.[7]

The overall experience with deferiprone has been encouraging and the drug has proved effective in decreasing iron overload in our thalassemic patients. The present results support the safety of L1 as an oral iron chelator in the dose we applied in our group (100 mg/kg bw/day). Other important questions related to chelation therapy (e.g., adequacy of iron burden control and worsening of fibrosis),[9] and possible interactions with other agents[10] are beyond the scope of this communication.

Contributions and Acknowledgments

All authors participated in regular meetings to review the protocol and data. YR planned the project and supervised its execution. RT arranged for data collection, recorded observations and follow-up. Manolis K was responsible for ophthalmic studies. CZ and PK responsible for radioisotopic ventriculography. VK and SS were responsible for clinical chemistry data. AA was responsible for echocardiographic and ECG data. NS and Markissia K were responsible for data analysis and statistical analysis. KK prepared the first and second drafts of the report, to which all authors contributed comments and interpretations of results. DL was responsible for the final editing.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Potential implications for clinical practice

- Oral iron chelation therapy with deferiprone seems effective in stabilizing a negative iron balance at least in a portion of thalassemic patients who are unable or unwilling to use deferoxamine.
- According to present folllow-up data, on a small group of patients, deferiprone seems non toxic and well tolerated by practically all patients.
- Oral iron chelation is cost effective.
- This schedule is much more convenient than parenterally administered chelators.

Manuscript processing

Manuscript received May 26, 1999; accepted November 2, 1999.

References

1. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood 1997; 89: 739-61.
2. Olivieri NF, Brittenham GM, Matsui D, et al. Iron-chelation therapy with oral deferipronein patients with thalassemia major. N Engl J Med 1995; 332:918-22.
3. Hoffbrand AV, AL-Refaie F, Davis B, et al. Long-term trial of deferiprone in 51 transfusion-dependent iron overloaded patients. Blood 1998; 91:295-300.
4. Hershko C, Konijn AM, Link G. Iron chelators for thalassaemia. Br J Haematol 1998; 101:399-406.
5. Hoffbrand A. Iron chelation therapy. Curr Opin Hematol 1995; 2:153-8.
6. Kontoghiorghes GJ, Goddard JG, Bartlett AN, Sheppard L. Pharmacokinetic studies in humans with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one. Clin Pharmacol Ther 1990; 48:255-61.
7. Piperno A. Classification and diagnosis of iron overload. Haematologica 1998: 83:447-55.
8. 8. Mazza P, Amurri B, Lazzari G, et al. Oral iron chelating therapy. A single center interim report on deferiprone (L1) in thalassemia. Haematologica 1998; 83:496-501.
9. Olivieri NF, Brittenham GM, McLaren CE, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med 1998; 339:417-23.
10. Wonke B, Wright C, Hoffbrand AV. Combined therapy with deferiprone and desferrioxamine. Br J Haematol 1998; 103:361-4.