Original Articles

EFFICACY AND SAFETY OF ORAL IRON CHELATING AGENT DEFERIPRONE IN β-THALASSEMIA AND HEMOGLOBIN E- β THALASSEMIA

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ABSTRACT

Objectives: To assess efficacy and safety of oral iron chelating agent deferiprone (DFP) in patients with beta thalassemia and hemoglobin E-beta thalassemia.

Design: *Non-randomized study.*

Setting: Hematology Ottt-Patient Department.

Subjects: Forty-one patients of beta thalassemia and hemoglobin E-beta thalassemia.

Interventions: *DFP was given to 20 patients, 10 patients of beta thalassemia and 10 with hemoglobin E-beta thalassemia; the rest were taken as controls.*

Results: *A significant fall in serum ferritin was observed in the study group along with rise in urinary iron excretion ($p<0.05$). Adverse effects of DFP were nausea and vomiting (30%), significant arthropathy requiring stopping of the drug (30%), and reversible neutropenia in one patient. All these complications could be managed easily with medical supervision and no death or permanent disability was seen.*

Conclusions: *DFP is an effective and fairly well tolerated oral iron chelating agent. The side effects that occur can be tackled easily if monitored properly.*

Key words: *Beta thalassemia, Hemoglobin E-beta thalassemia, Ferritin, Deferiprone, Desferrioxamine.*

In Eastern India, both β-thalassemia (B-T) and hemoglobin β-P thalassemia (EB-T) are responsible for producing clinical picture of severe transfusion dependant thalassemia major(l,2). The treatment consists of giving regular blood transfusions and adequate chelation therapy for the ensuing iron overload. Till date, the only available iron chelator was desferrioxamine (DFX). However, there are certain major problems which limit the usefulness of DFX. These include the high cost of the drug, poor patient compliance due to its parenteral route of administration and the high cost of the infusion pump necessary for injection. Thus, there is a pressing need for the introduction of an effective and safe oral iron-chelating agent for these patients. Amongst the oral iron-chelating

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agents, the compound 1,2 dimethyl-3-hydroxypyrid 4-one or deferiprone (DFP)(3), previously known as LI, has been studied most extensively. Clinical trials in several centres have demonstrated that DFP is an effective iron chelating agent with minimal toxicity(4-7). The present study was undertaken to evaluate the efficacy and safety of oral DFP in transfusion dependant B-T and EB-T patients in Eastern India.

Material and Methods

Forty one patients with transfusion dependent thalassemia, 22 BT and 19 EB-T were taken up for the study. Approval for the clinical trial was obtained from the Ethical Committee of Kothari Medical Centre as well as the Food and Drug Administration of India through Cipla Company. Diagnosis was at first established on the basis of peripheral blood picture, level of fetal hemoglobin and hemoglobin electrophoresis(2). Patients between 4 and 27 years age with ferritin levels between 1000 ng/ml and 8000 ng/ml were chosen for the study, if they were negative for HBsAg and HIV-antibody by ELISA techniques. Among these patients, 20 patients (10 B-T and 10 EB-T) were taken as the study group and 21 (12 B-T and 9 EB-T) were considered as the control group. The initial patient data is given in *Table I.* All patients were treated in a similar manner with packed red cell transfusions approximately at intervals of 3-5 weeks to keep pre-transfusion hemoglobin around 10 g/dl as far as possible. Seriously ill patients with cardiac complications, overt diabetes mellitus or HIV-positivity were excluded from the study. The control group was allowed to take subcutaneous DFX as it was considered unethical to discontinue it's usage.

DFP was started orally in the study group with a dose of 37 mg/kg/day and was gradually increased to 75 mg/kg/

TABLE I-*Initial Patient Data*

Parameter	Treatment (n=20)	Control (n=21)
Age (yr)	10.6 ± 6.4 [4:27]	7.3± 4.6 [4-17]
Male: Female	15:5	12:9
Age at diagnosis (mo)	21.9±20.9	29.9±2.5
Liver size (cm)	3.0 ±1.4 [0.5-7]	2.5±1.1 [1-5]
Spleen size (cm)	3.6±1.5 [2-7]	2.8±1.4 [1-6]
Splenectomy	9	3
Previous chelation therapy (desferrioxamine)	15	12

Figures in parenthesis indicate range

day over a period of 30-40 days. This was given as 500 mg capsules in 2-4 divided doses. The control group was allowed to continue with DFX if they could afford. All patients were discouraged to take any medicine besides folic acid, 5-10 mg/day.

Initial investigations done included blood counts, liver function tests, lipid profile, calcium, phosphorus, urea, creatinine, uric acid and fasting sugar. In view of the known rheumatological problems with DFP, Coombs test, rheumatoid factor (RF), LE cell test and antinuclear factor (ANF) were done. Electrocardiogram, chest X-ray and virological status including hepatitis B-surface antigen and HIV antibody were checked at the start of study. The body iron status was monitored by measuring serum iron and total iron binding capacity (TIBC), ferritin, 24 h-urinary iron excretion by atomic absorption spectrophotometry. In the first month, all patients were examined every 10 days and subsequently during every clinic visit. Complete blood count and serum ferritin were measured every month. After 3,6,9 and 12 months the entire initial evaluation was repeated.

Serum ferritin was assayed by ELISA method (Quantum II abbott; Bio-Merioux, France). Urinary iron excretion was measured by atomic absorption spectrophotometry (Perkin Elemer, Model No. 2380) at the Department of Metallurgy, Jadavpur University. ANF was evaluated by immunofluorescence technique. Antibody to ds-DNA was assayed by ELISA Kit (Sigma, Nicco Biotech). Biochemical tests were performed by routine methods (Hitachi 704, Boehringer 4020). Statistical evaluation was done by the Students' t test.

Results

Initial mean serum ferritin was 3358 ± 1613 ng/ml in the study group and decreased significantly to 1525 ± 927 ng/ml while that of control group was 2174 ± 1526 ng/ml and remained at 2183 ± 1687 ng/ml after a period of 12 months *(Table II).* The drop in serum ferritin correlated significantly with the initial serum ferritin level ($p < 0.05$). The urinary iron excretion showed significant rise while on DFP as compared to the initial value in the study group ($p < 0.005$). All patients noticed red urine at the time of taking the drug. Details of urinary iron excretion before starting and 12 months after starting DFP are shown in *Table III.*

All study patients noticed initial lightening of skin pigmentation. In 2 E-BT patients, this was followed by darkening after 2 months of taking the drug although the serum ferritin did not show any rise. All patients receiving DFP showed weight gain (0.5 to 10 kg).

Toxicity of DFP

Minor gastrointestinal side effects in the form of nausea (6 patients) and occasional vomiting (2 patients) were initially reported by 6 out of 20 patients (30%). The severity decreased with time and no specific treatment was required.

In the study group, 5 B-T patients developed joint pain involving mainly hips and knees and in one case the shoulder joint. The joints were painful with restriction of movement; warmth and effusion was seen in 3 cases. The patients were unable to squat on the floor and use an Indian-style toilet. One of these patients also complained of pain in the interphalangeal joints. All these patients

TABLE II—*Serum Ferritin in Thalassemia Patients*

	Initial Mean ± SD (ng/ml)	At the time of evaluation Mean ± SD (ng/ml)
Trial		
B-T	3763 ± 1404 (n=10)	1956 ± 851 (n=5)
EB-T	2948 ± 1771 (n=10)	1166 ± 894 (n=6)
Total	3358 ± 1613 (n=20)	1525 ± 927 (n*=11)
Control		
B-T	2231 ± 1435 (n=12)	2270 ± 1582 (n=12)
EB-T	2062 ± 1793 (n=9)	1943 ± 1670 (n=9)
Total	2174 ± 1526 (n=21)	2183 ± 1687 (n=21)

B-T : β-thalassemia; EB-T: Hemoglobin E-β thalassemia

TABLE III—*24-h Urinary Iron Excretion*

Diagnosis	Initial Mean ± SD (mg/d)	At the time of evaluation Mean ± SD (mg/d)
Trial		
B-T	0.88 ± 1.29 (n=10)	13.10 ± 3.57 (n=5)
EB-T	1.93 ± 2.11 (n=10)	16.50 ± 8.27 (n=6)
Total	1.41 ± 1.56 (n=20)	14.95 ± 6.51 (n*=11)
Control		
B-T	0.86 ± 1.23 (n=11)	1.27 ± 0.70 (n=11)
EB-T	2.61 ± 2.19 (n=6)	3.90 ± 2.26 (n=7)
Total	1.48 ± 1.78 (n=17)	2.29 ± 1.96 (n*=18)

B-T : β-thalassemia; EB-T: Hemoglobin E-β thalassemia

were negative for LE cells, ANF and anti Ds-DNA throughout the period of study. One of these 5 patients had positive RF at the beginning of the study, while 3 developed positive RF during the study. Another patient with positive RF never developed joint pain. Two patients who developed joint pain were negative for RF throughout the period of study. One EB-T patient developed pain in the ankle joints which subsided after discontinuing the drug. The B-T patients were more prone to develop joint pain as compared to the EB-T as well as the controls ($p < 0.05$). Joint pain necessitated stopping of DFP in 5 B-T patients. In one

patient, DFP could be restarted after pain subsided. However, in 4 patients, the drug could not be restarted due to reccurrence of joint pain. Three patients with B-T on treatment with DFX showed joint pain although 5 patients had positive RF. The relationship of ESR, RF and joint pain is shown in *Table IV*.

The blood counts remained within normal range in all the patients upto 11 months of study inspite of febrile episodes which subsided uneventfully in all cases and did not require hospitalization. One E-BT patient on DFP underwent an emergency appendicectomy which proceeded without complications. One patient developed chicken pox after 4 months on DFP and the drug was stopped temporarily. Recovery was uneventful and he continued to take DFP after that. At the end of eleven and half months of taking DFP, one BT patient presented with neutropenia (absolute neutrophil count 290/cumm) with fever for 7 days and striking gingival infection. The bone marrow done at this time showed arrest of granulopoiesis in the myelocyte stage. The febrile episode could be managed within 3 days with ciprofloxacin and metronidazole and the neutrophil count normalized within 7 days of stopping DFP.

The biochemical parameters of renal and hepatic function were stable in all cases. One patient with elevated liver enzymes (serum GPT 360 U/L), and a positive hepatitis C antibody did not show any further deterioration of the liver function while on DFP. No ophthalmological problem was seen in these patients. One patient developed excessive spitting which was diagnosed as obsessive compulsive behavioral disorder which did not disappear despite discountinuing the drug.

Drop Outs

Patients stopped taking DFP during the study period for various reasons. In 5 B-T patients the drug had to be stopped for joint pain. It could be restarted in 1 patient. Similarly, 1 EB-T patient had joint pain and stopped the drug herself after coming to know that her ferritin level had dropped. In another patient, DFP was stopped after ferritin level came down to 250 ng/ml after 9 months following which he was given DFP for 7 days after each transfusion to keep the ferritin level at steady state. In

TABLE IV—*Relation between ESR, Rheumatoid Factor Positivity and Joint Pain*

ESR (mm at 1 h)	Initial			6 months			Latest evaluation		
	Total	RF	JP	Total	RF	JP	Total	RF	JP
≤20	22	02	0	19	07	01	22	01	0
21-40	15	01	0	12	01	02	10	02	01
41-80	03	01	0	07	0	02	03	0	01
>80	01	0	0	01	01	01	02	01	0
Total	41	04	0	39	09	06	37	04	02

RF = rheumatoid factor; JP = joint pain

one patient each, DFP had to be stopped for appendicectomy and chicken pox temporarily. No systemic lupus erythematosus type of syndrome was seen.

Discussion

The search for a cheap and orally administrable iron-chelator which would simplify the management of thalassemia patients is continuing. Many oral iron-chelating agents are undergoing evaluation at present, out of which DFP has been studied most extensively(3)-. The efficacy of DFP has been established in animal models as well as in several clinical trials(4-7) in many countries.

This drug proved effective in the dosage of 75 mg/kg body weight in reducing the iron-overload of thalassemics from Eastern India as evidenced by a significant fall in serum ferritin and rise in urinary iron excretion. These data corroborate those reported in previous studies(4-7). In one EB-T patient, the fall in serum ferritin was so marked that he could be maintained at this level with short courses of DFP. A similar fall has been reported in one EB-T patient from Switzerland(7). Our control patients on DFX did not show a comparable fall in serum ferritin mainly because of the extremely irregular and inadequate dosage of the drug administered. The rise in serum ferritin level in the control patients was low because they tried to take DFX as much as possible (at a dose of 10-40 vials of 500 mg injection per month).

The most frequent side-effects were nausea and vomiting and arthropathy (30%); the latter necessitating withdrawal of the drug in 6 cases. Arthropathy related to the use of DFP has been reported in all other previous studies(4-7) for which no immunological cause has been documented. No major infection was seen in these patients and one patient recovered uneventfully from appendicitis and another from chicken pox while on DFP. Neutropenia with accompanying infection was observed in one patient (5%) which was completely reversible within a short span of time and did not recur with rechallenging by the drug despite medical advice. Several cases of neutropenia or agranulocytosis have been reported in the literature so far(8), including one case from Bombay. No other serious adverse effects or other biochemical disturbances were recorded with the use of the DFP in this dosage. No patient developed symptoms akin to systemic lupus erythematosus, as reported previously (9).

In conclusion, it may be said that DFP is effective and fairly well tolerated oral iron-chelating agent in most of our patient from Eastern India. The alternative treatment in the form of subcutaneous DFX is practically not applicable to our patients as they cannot afford to take adequate dosage of the drug. Though adverse side-effects may occur, it is possible to monitor these patients carefully so as to keep these at a minimum and at the same time achieve a negative iron balance. Considering the fact that inadequate chelation may lead to death in the second to third decade of life(10), the side effects associated with DFP use should be carefully looked for and the drug prescribed under careful medical supervision.

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