EFFICACY AND ADVERSE EFFECTS OF ORAL IRON CHELATOR DEFERIPRONE (L1, 1,2- DIMETHYL-3-HYDROXYPYRID-4-ONE) IN PATIENTS WITH BETA THALASSAEMIA MAJOR IN PAKISTAN

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Background: Deferiprone (DFP,L1) is a bidentate oral iron chelator which binds to iron in a 3:1 ratio. It has the potential advantage of reduced cost and increased compliance. We conducted a study in order to determine the efficacy and adverse effects of DFP in Pakistani thalassaemic patients. **Methods:** A group of 26 thalassaemic patients entered the study during the period Jan 1999 to Aug 2002. DFP supplied by Lipomed, Switzerland was given at a daily dose of 75 mg/kg/day (range 50-75 mg/kg/day). After giving informed written consent all the patients were subjected to clinical examination and investigations for monitoring the response. Blood complete picture, liver function tests, blood urea & creatinine, antinuclear factor antibodies (ANF) were tested in all cases before starting DFP treatment. **Results:** The patients ages ranged from 11 to 27 years, 16 were male and 10 were female. Initial serum ferritin level ranged from 3100-8800 μg/l, mean serum ferritin level was 7129±1467 μg/l (95% CI 6536 – 7721 μg/l). ECG and Echocardiography was performed in all cases and in 11 cases Cardiac Multigated acquisition (MUGA) Scan was also performed and six patients with impaired left ventricular function were identified. Four patients were lost to follow up and one patient died due to cardiomyopathy. Among the remaining 21 patients serum ferritin levels dropped to 1900μg/l to 5600μg/l with mean level of 4288 μg/l (95%CI 3874 – 4702 μg/l), SD 911 μg/l. Significance of difference was ($p < 0.001$) by Paired samples 't' test. Six patients had gastrointestinal symptoms along with two having arthropathy. ANF positivity was not detected in any patient while on DFP treatment. Similarly, agranulocytosis was not detected in any patient. C**onclusion**. Mean serum ferritin level estimated at the start of trial was 7129 μg/l. This shows that Pakistani thalassaemic patients are quite iron overloaded due to socioeconomic reasons that are peculiar to our setup. In this study DFP was well tolerated and caused fewer side effects. It had much better patient compliance and was effective in lowering serum ferritin level in previously most poorly chelated patients.

Keywords: Thalassaemia, Deferiprone, Transfusion iron overload, Cardiomyopathy, Demography

INTRODUCTION

Thalassaemia is the most common genetic disorder in Pakistan.[1,2] It is estimated that over 5000 thalassemic homozygotes are born in Pakistan each year.[3] The mainstay of therapy in thalasaemia major is packed red cell transfusions. Each 500 ml of transfused blood contains bout 250 mg iron. Iron overload caused by transfusion is inevitable unless chelation therapy is given. Transfusion haemosiderosis is now the major cause of late morbidity and mortality in thalssaemia major in developing countries like Pakistan.[4]

There is massive outpouring of iron in blood in poorly chelated thalassaemia major patients overwhelming the iron carrying capacity of transferrin, resulting in the emergence of toxic non-transferrin bound iron (NTBI).[5,6] NTBI is a potentially toxic component of plasma iron that result in free radical generation causing tissue damage.[7] In thalassaemic patient who are not receiving iron chelation therapy, the accumulation of iron will progress relentlessly and when 20-25 grams of iron has been acquired, clinical manifestations of iron toxicity may become evident. Iron damages the heart, liver, the endocrine organs (with failure of growth, hypothyroidism, hypoparathyriodism, diabetes mellitus, delayed or absent puberty). Excess of melanin and haemosiderin deposition in skin gives a slatey gray appearance.[8]

Endocrine problems caused by direct accumulation of iron in endocrine glands or indirectly through the hypothalamic pituitary axis are common. These problems are rarely reversible. Myocardial siderosis is the single most important cause of mortality in inadequately treated thalassaemia patients.[9] In the absence of intensive iron chelation death occurs in the second or third

decade usually from congestive cardiac failure and life threatening arrhythmias.[10]

Liver disease is caused by direct accumulation of iron, however the coexistence of chronic hepatitis C or B with an incidence of >50% in thalassaemic patients in our country underlines the complexity of this problem.[11]

Since there is no physiological way to induce significant excretion of iron, pharmacological removal by the administration of an iron chelating agent is used to help forestall iron overload. Desferrioxamine (DFO), a highly specific iron binding hydroxamic acid is the standard treatment. Improved survival in well chelated thalassaemic patients has been reported in several major studies from the Italy, UK and North America. The strongest direct evidence supporting the beneficial effects of DFO on haemosiderotic heart disease is the reversal of established cardiomyopathy in some far advance cases.[8]

DFO is an extremely expensive drug for use on long term basis and ineffective when given orally and it is also only effective in achieving negative iron balance when administered by sub-cutaneous infusion requiring an expensive pump. These shortcomings have made DFO virtually an impossible drug for Pakistani thalassaemia major patients.

The need for an orally effective iron chelator led to the discovery of DFP.[12,13] Combined experience of four major European and Canadian groups pioneering the clinical use of DFP has been described in a report of the International Study Group of Oral Iron Chelator (ISGOIC). Major side effects include agranlocytosis, arthritis and skin changes secondary to zinc deficiency.[14]

A clinical trial has been conducted in which DFP has been given to thalassaemia major patients registered at Thalassaemia centre, Rawalpindi to establish efficacy and side effects of DFP in our population.

MATERIAL AND METHODS

This clinical trial was carried on a cohort of 26 transfusion dependant patients of thalassaemia major already registered at Thalassaemia Centre Rawalpindi during the period Jan 1999 to Aug 2002. They were treated with DFP 75 mg/kg/day (range 50-75 mg/kg/day) supplied by Lipomed, Switzerland. All patients were prescribed zinc supplements. Patients below 10 years of age were not enrolled in the trial. Informed written consents were obtained from parents after explaining possible advantages and side effects of DFP. Blood complete picture, blood glucose, serum calcium, liver function tests, blood urea & creatinine, antinuclear factor (ANF) were tested in all cases using routine laboratory methods before starting DFP. Serum ferritin was estimated by chemiluminescence technique using hormone autoanalyser Immulite 2000 (DPC-USA). Similarly patients with ANF positivity were not included in the trial. ECG and echocardiography was performed in all cases. Scintigraphic assessment of left ventricular function using Multigated acquisition (MUGA) scan with Technitium-99m as the tracer was also performed in 11 cases. Impaired left ventricular function was found in six cases due to iron overload. Blood counts were monitored initially at weekly interval then after every 4 weeks along with liver function test, blood urea and creatinine level. The data was entered into Statistical Package for Social Sciences (SPSS) version 11.0 and was analyzed. Paired samples 't' test was used to compare pre and post chelation serum ferritin levels.

RESULTS

Analysis of the demographic data of the patients showed that the patients ages ranged from 11 to 27 years with 16 male and 10 female patients. Sixteen, nine and one patients belonged low, middle and high socioeconomic status respectively (Table 1). Originally 11 patients were subjected to cardiac MUGA scan and six patients were identified as having impaired cardiac function (Fig 1). One of them died due to cardiomyopathy and in the remaining five individuals cardiac MUGA scan was repeated after nine months which did not reveal significant improvement in left ventricular function and DFO was started alongwith DFP.

Initial serum ferritin level ranged in the cohort of 26 patients from 3100 μg/l to 8800 μg/l, mean serum ferritin level was 7129 μg/l (95% Confidence Interval of mean (CI) 6536 – 7721 μg/l), standard deviation (SD) 1467 μg/l. Four patients were lost to follow up and one patient died due to cardiomyopathy. Among the remaining 21 patients serum ferritin levels dropped to 1900μg/l to 5600μg/l with mean level of 4288 μg/l (95%CI 3874 – 4702 μg/l), SD 911 μg/l. This is graphically depicted by a box-whiskers plot (Fig 2). Significance of difference was ($p < 0.001$) by Paired samples 't' test. DFP was well tolerated, had good patient compliance and was found to have a highly acceptable safety profile. Only six patients had gastrointestinal symptoms along with two having arthropathy. ANF positivity and skin changes were not detected in any patient while on DFP treatment. Similarly, agranulocytosis was not

detected in any patients (Table 2). Four patients were lost to follow up and one patient died

Table-1: Important demographic data of patients

Socioeconomic class	Male	Female	Total
Low	9 (34.6 %)	7 (26.9 %)	16 (61.5 %)
Middle	6 (23.1 %)	3 (11.5 %)	9 (34.6 %)
High	1 (3.8 %)	0	1 (3.8 %)
Total	16 (61.5 %)	10 (38.5 %)	26 (100 %)

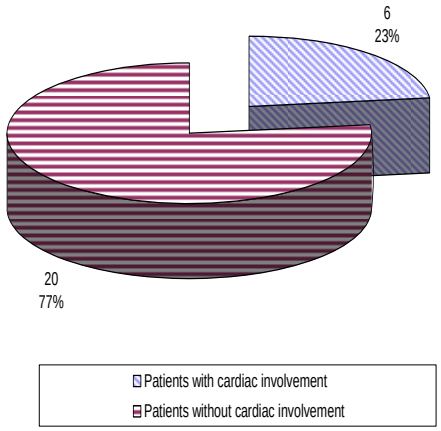

Fig 1 Prevalence of cardiomyopathy demonstrated by cardiac MUGA scan

DISCUSSION

In Pakistan over 5000 thalassaemic homozygotes are born each year.[1] There exist inadequate treatment facilities available for this large number of thalassaemic children. This is in sharp contrast with the scenario in developed parts of the world where emphasis is on curative forms of therapy, such as allogeneic bone marrow transplantation. This requires a highly developed medical infrastructure with sophisticated scientific facilities and availability of enormously costly medications.[15] Unfortunately this is beyond reach of majority of our thalassaemic patients and our patients have to resort to conventional therapy comprising principally of blood transfusions and iron chelation therapy. Majority of our children receive inadequate chelation therapy as we have seen in this study. Mean serum ferritin level estimated at the start of trial was 7129 µg/l. This shows that Pakistani thalassaemic patients are quite iron overloaded. The reasons contributing to this scenario include low socioeconomic status, lack of patient and family education regarding their disease, non conformity with DFO due to its high cost, cost of pump and inconvenience caused to the patient and family.

Iron chelation is the one of the mainstay of conservative management. DFO is the first choice approach for iron chelation. Intensive chelation therapy with DFO can reverse heart damage due to iron overload. However, the cost of the drug precludes its use in our thalassaemic patients. Moreover, DFO is only effective in achieving negative iron balance when administered by continuous subcutaneous infusion requiring an expensive battery operated pump. The need for an orally effective iron chelator led to the discovery of a compounds 1-2-dimethyl-3-hydroxypyridin-4-one (L1, CP20) now known as DFP. DFP has been studied extensively and several clinical trials have been reported. DFP 75 mg/kg/day has been shown as effective as DFO 30-40 mg/kg/day in promoting iron excretions in iron- loaded patients.[16-19]

Table 2: **Observed side effects of Deferiprone during the trial**

Side effect	No of patients (n=21)
Gastrointestinal symptoms	6 (28.6 %)
Arthropathy	2 (9.5 %)
Skin changes	0
Agranulocytosis	0
ANF positivity	0

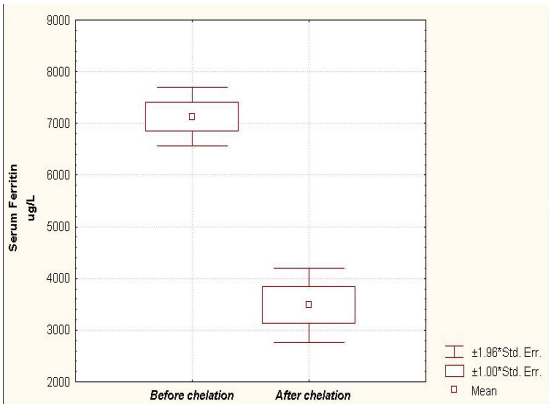

Fig 2 Serum ferritin levels at beginning and end of trial (p<0.001)

In this study DFP has proved an effective iron chelator as serum ferritin level was significantly reduced. Side effects of DFP noted in different clinical trials are neutropenia, nausea, zinc deficiency and arthropathy. Agranulocytois

was not observed in this study. Similarly ANF positivity and skin changes secondary to zinc deficiency were not detected in any patients. DFP has proved an effective and largely safe iron chelator in this study. Further studies are required to evaluate efficacy of DFP to decrease iron contents of liver, heart and endocrine organs in comparison to DFO in iron-overloaded patients. As our thalassaemia major patients are heavily iron over loaded, we therefore recommend combined use of DFO and DFP to reverse cardiac damage.[20]

CONCLUSION

In this study the drug was well tolerated and caused fewer side effects. It had much better patient compliance and was effective in lowering serum ferritin level in previously most poorly chelated patients.

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