

# Experience with the oral iron chelator deferiprone in transfusion-dependent children

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## Abstract

**Objective** To establish efficacy and safety of deferiprone.

**Design** Prospective study.

**Setting** The Lady Ridgeway Hospital for Children, Colombo.

**Patients** Transfusion-dependent children in the age group 1 to 15 years.

**Intervention** Patients were given 75 mg/kg/day of deferiprone orally in divided doses.

**Measurements** Efficacy of deferiprone therapy was assessed by 4 to 6 monthly serum ferritin (SF) assays. Safety of therapy was assessed by 4-weekly white cell counts and serum alanine aminotransferase (ALT) levels. The Z-score was used to assess the significance of the difference between the mean initial and final SF level.

**Results** 82 patients received deferiprone therapy for a mean duration of  $30 \pm 14$  months. Initial SF levels ranged from 1115 to 12 165  $\mu\text{g/l}$  with a mean of  $5156 \pm 2631 \mu\text{g/l}$ . Final SF levels ranged from 312 to 15 285  $\mu\text{g/l}$  with a mean of  $2809 \pm 2380 \mu\text{g/l}$  (Z score 5.99;  $p < 0.001$ ). Two (2.4%) children developed agranulocytosis which reverted to normal on discontinuation of treatment. 41 (50%) developed arthropathy and in 17 this was severe enough to require discontinuation of therapy. Serum ALT levels were raised in 35 (43%) patients but reverted to pretreatment values or lower despite continuation of deferiprone therapy. There was one death in a 9-year old child who developed diabetes mellitus and heart failure despite deferiprone therapy for 3 years.

**Conclusions** A final SF level  $< 2500 \mu\text{g/l}$  was achieved in 52% children. Severe arthropathy and agranulocytosis may necessitate permanent discontinuation of therapy.

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During the initial year of study, the serum ferritin assay kits were purchased by Cipla Pharmaceuticals India, and given to the Biochemist MRI who supervised the estimations. This is acknowledged in a previous article (CMJ, 2000; 45: 71-4). For the last 3 years the SF estimations have been done by the Radio Immunoassay Laboratory of the National Hospital, Sri Lanka. Deferiprone is directly purchased by State Pharmaceuticals Corporation and given through the Medical Supplies Division. The authors have no competing interests and no sponsors.

## Introduction

Desferrioxamine is a safe and effective iron chelator (1). However, it is expensive and has to be given parenterally resulting in significant non-compliance (2). Long term therapy with the orally active iron chelator, deferiprone, induces a sustained decrease in body iron in the majority of thalassaemia major patients unable or unwilling to receive desferrioxamine (3). Agranulocytosis and arthropathy account for nearly all the withdrawals from deferiprone therapy (4). We undertook a prospective study of deferiprone in children unable or unwilling to use parenteral desferrioxamine. A preliminary assessment of this on-going study was made at the end of one year (5).

## Methods

Children, 1 to 15 years of age, with transfusion-dependent anaemia, who were unable or unwilling to use parenteral desferrioxamine, formed the study population. 5 paediatric units of the Lady Ridgeway Hospital were involved in the study which was approved by the ethical review committee of the Faculty of Medicine, Colombo. Written informed consent was obtained from the parent of each child.

Patients were given deferiprone 75 mg/kg/day in 2 to 3 divided doses. Efficacy of therapy was assessed by 4 to 6 monthly serum ferritin (SF) assays. During first year of study, SF assays were done using ELISA technique (5). Subsequently SF estimated by radio-immunoassay at National Hospital of Sri Lanka (NHSL). Safety of deferiprone was assessed by 4-weekly white cell counts and serum alanine aminotransferase (ALT) levels.

The Z-test was used to test the significance of the difference between mean initial and final SF levels. A Z score  $> 3.08$  is extremely significant ( $p < 0.001$ ), 2.58-3.08 definitely significant ( $p < 0.01$ ), 1.96-2.57 probably significant ( $p < 0.05$ ) and  $< 1.96$  not significant.

## Results

There were 82 transfusion-dependent children of whom 47 were boys. 44 were 1 to 5 years of age, 26 were 6 to 10 years and 12 were 11 to 15 years.

44 children had homozygous  $\beta$  thalassaemia, 8 had HbE/ $\beta$  thalassaemia 1 had HbS/ $\beta$  thalassaemia. 17 had

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congenital dyserythropoietic anaemia, 1 had sideroblastic anaemia and 11 had chronic haemolytic anaemia of unknown aetiology.

Duration of therapy was <12 months in 9 patients, 12 to 24 months in 24, 25 to 36 months in 15, and 36 to 49 months in 34 patients. Mean duration of therapy was  $30 \pm 14$  months.

Two or more SF estimations were obtained in all patients. Initial SF ranged from 1115 to 12 165  $\mu\text{g/l}$  with a mean of  $5156 \pm 2631 \mu\text{g/l}$ . Final SF ranged from 312 to 15, 285  $\mu\text{g/l}$  with a mean of  $2809 \pm 2380 \mu\text{g/l}$  (Z score 5.99;  $p < 0.001$ ). Correlation between initial SF and number of patients with final SF <2500  $\mu\text{g/l}$  is shown in Table 1. In 52% children the final SF was <2500  $\mu\text{g/l}$ . 33 (67%) of these children had an initial SF <5000  $\mu\text{g/l}$ . The number of patients showing different percentage reductions in the SF is shown in Table 2. 60 (73%) children had >25% reduction in SF and 38 (46%) had >50% reduction in SF.

**Table 1. Correlation between initial SF and number of patients with final SF < 2500  $\mu\text{g/l}$**

Initial SF ( $\mu\text{g/l}$ )	Number of patients	Number of patients with final SF <2500 $\mu\text{g/l}$ (%)
<2500	15	14 (93)
2500-5000	26	19 (73)
>5000	41	16 (39)

**Table 2. Number of patients showing different percentage reductions in SF**

% reduction of SF	Number of patients (%)
Nil	10 (12)
1-25	12 (15)
26-50	22 (27)
>50	38 (46)

2 (2.4%) children developed agranulocytosis (neutrophils  $<0.5 \times 10^9/\text{l}$ ). In the first case the neutrophil count spontaneously reverted to normal within 10 days of stopping deferiprone. In the second case granulocyte colony stimulating factor was given and the neutrophil count reverted to normal within 1 week. Deferiprone was not re-started in both.

41 (50%) children developed arthropathy. In most cases this responded to ibuprofen therapy with or without a reduction of the dose of deferiprone. However, in 17 (41%) children deferiprone was permanently withdrawn. 37 (90%) children with arthropathy had initial SF levels >2500  $\mu\text{g/l}$ .

Serum ALT levels were raised on one or more occasions in 35 (43%) patients but reverted to pre-treatment values or lower despite continuation of deferiprone therapy. All 35 children with raised ALT levels had initial SF >2500  $\mu\text{g/l}$ .

#### Drop-outs

Deferiprone was discontinued in 19 patients, 17 because of severe arthropathy and 2 because of agranulocytosis. 4 patients voluntarily dropped out after several months. From January 2001, the Health Ministry permitted deferiprone to be used in any government hospital under the supervision of a paediatrician. 8 patients requested referral to Polonnaruwa Hospital and 1 to Colombo North Teaching Hospital for continuation of deferiprone therapy.

#### Deaths

Death occurred in a 9-year old boy with chronic haemolytic anaemia receiving monthly blood transfusions from the age of 3 months. Despite deferiprone therapy from May 1998 to May 2001, there was only a small reduction of SF (initial SF 8586  $\mu\text{g/l}$ ; final SF 7860  $\mu\text{g/l}$ ). He developed diabetes mellitus and heart failure in January 2001. In May 2001 he was hospitalised with a left-sided pleural effusion and clinical evidence of heart failure. He was transferred to the cardiothoracic unit of the NHSL where he developed a cardiac arrest during pleural aspiration and died 2 days later.

#### Discussion

Measurement of liver iron content (LIC) is a better indicator of iron overload than SF estimation (6). However, liver biopsy is invasive and LIC assay is not available in Sri Lanka. There is good correlation between SF and LIC especially when SF is <2500  $\mu\text{g/l}$  (6). It has been suggested that deferiprone may lose its efficacy after a number of years (7). However in our study the mean SF declined significantly over a mean duration of  $30 \pm 14$  months.

Patients whose SF was maintained at 2500  $\mu\text{g/l}$  or less had a 91% survival rate without cardiac disease at 15 years (1). In about 70% of thalassaemic patients treated with deferiprone for over 2 years, SF decreased and remained <2500  $\mu\text{g/l}$  (3). In our series, 52% patients had a final SF <2500  $\mu\text{g/l}$ . Furthermore, in 73% patients the percentage reduction of SF exceeded 25 and in 46% exceeded 50. Thus efficacy of deferiprone is established for the treatment periods given in the results section.

The most dangerous toxic effect of deferiprone is agranulocytosis which appears to be fully reversible on cessation of the drug. In our series 2 children developed agranulocytosis and both recovered, one spontaneously and the other with granulocyte colony stimulating factor.

The most common clinical problem associated with deferiprone therapy is arthropathy consisting of musculoskeletal stiffness, joint pain and joint effusion primarily affecting large joints (9). It has been postulated that



arthropathy could be secondary to the redistribution of iron into the synovial membrane or cartilage (2). In our series 50% children developed arthropathy necessitating permanent cessation of therapy in 41% of them. In the Indian trial incidence of arthropathy was greatest in the most iron-loaded patients receiving the largest dose of deferiprone (100 mg/kg/day) (2). In our study all patients received 75 mg/kg/day. However iron-loading may be a factor as 90% occurred in patients whose initial SF exceeded 2500 µg/l.

Fluctuations in liver function during deferiprone therapy have been reported from several centres (10, 11). In our series the serum ALT levels were transiently elevated in 43%. Raised ALT levels correlated well with increased iron load, none having SF <2500 µg/l. 27% children showed little or no reduction of SF with deferiprone therapy. One study suggests that increasing the dose of deferiprone to 100 mg/kg/day or combination of deferiprone with desferrioxamine may be successful in these cases (12).

### Conclusions

Overall efficacy of deferiprone therapy is established during the treatment periods stated above. A final SF level <2500 µg/l was achieved in 52% children. Severe arthropathy and agranulocytosis may require permanent discontinuation of therapy.

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