Paper

A trial of deferiprone in transfusion-dependent iron overloaded children

G N Lucas, B J C Perera, E A N Fonseka, D D S De Silva and M Fernandopulle

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(Key words: Efficacy, safety, adverse effects)

Abstract

Objective To determine the efficacy and safety of deferiprone.

Design Prospective study.

Setting 5 paediatric medical units at the Lady Ridgeway Hospital for Children (LRHC), Colombo.

Patients Transfusion-dependent iron overloaded children in the age group 2 to 15 years.

Intervention Patients were given a total daily dose of 75 mg/kg of deferiprone orally in divided doses.

Measurements Efficacy of deferiprone therapy was assessed by 4-monthly serum ferritin assays using the ELISA technique. Safety of deferiprone therapy was assessed by 4-weekly white cell counts, platelet counts and serum transaminase levels. The Z-test was used to assess the significance of the difference between the mean initial serum ferritin level and the mean subsequent serum ferritin level.

Results 54 patients received deferiprone therapy for a mean duration of 9 ± 3 months. Initial serum ferritin levels ranged from 1500 to 10 700 ng/ml with a mean of 5743. Subsequent serum ferritin levels, obtained in 48 patients ranged from 740 to 7300 ng/ml with a mean of 3558 ($p<0.001$). In 47 of the 48 patients subsequent serum ferritin levels were lower than initial levels. One child developed severe neutropaenia, which reverted to normal on discontinuation of treatment. 11 children developed arthropathy, which responded to ibuprofen therapy combined in some cases with a reduction of the dose of deferiprone to 50 mg/kg/day. Serum transaminase levels were raised in 5 patients but reverted to pretreatment values or lower despite continuation of deferiprone therapy.

Conclusions Deferiprone is a safe and effective oral iron-chelating agent which can be used, under strict supervision, in transfusion-dependent iron overloaded children.

Introduction

In patients with thalassaemia major and other transfusion-dependent anaemia, a regular transfusion program sustains growth and development during childhood, but without concomitant chelation therapy, iron from the transfused red cells accumulates inexorably (1). Excess iron damages the liver, endocrine organs and heart, and may be fatal by adolescence (2). Several studies have demonstrated that treatment with parenteral desferrioxamine can prevent the complications of iron overload and improve survival in thalassaemia major (3,4). Some patients are unable or unwilling to receive parenteral desferrioxamine treatment because of allergy, toxic effects, an inability to comply with prolonged parenteral infusions or non-availability of the drug. A possible alternative to desferrioxamine, the orally active iron-chelating agent deferiprone, has undergone preliminary evaluation in the United Kingdom, Canada, Europe and India (5,6,7,8). Studies using the serum ferritin concentration as an indirect estimate of the body iron load suggest that the drug is effective, but in some patients treated with deferiprone, reversible neutropaenia or agranulocytosis has developed (9). We report the results of a prospective study of deferiprone in children unable or unwilling to use parenteral desferrioxamine.

Material and methods

Children with thalassaemia major and other transfusion-dependent anaemias who were unable or unwilling to use parenteral desferrioxamine and who were in the age group 2 to 15 years were enrolled in the trial. Each child received transfusions at 3 to 4 week intervals to maintain the haemoglobin concentration at a level above 10 g/dl. No parenteral desferrioxamine was given to any of the children during the course of the trial. Five paediatric medical units at the LRHC were used in the study, which was approved by the ethical review committee of the Medical Faculty, Colombo. Written informed consent was obtained from the parent of each child.

Patients were given a total daily dose of 75 mg/kg of deferiprone to be taken orally every 8 to 12 hours. Efficacy of deferiprone therapy was assessed by 4-monthly serum ferritin assays using the ELISA technique. Separation of plasma was performed at the Medical Research Institute and the LRHC, and the serum ferritin assayed at the Durdan's hospital, Colombo.

All authors are Paediatricians at Lady Ridgeway Hospital for Children, Colombo. *(Revised version accepted 18 December 1999).*

Safety of deferiprone was assessed by 4-weekly total and differential white blood cell counts, platelet counts and serum transaminase levels.

The statistical method used to test the significance of the difference between the mean initial serum ferritin level and the mean subsequent serum ferritin level was the Z Test. An Z score of 3.09 or more is extremely significant ($p<0.001$); a score of 2.58 or more is definitely significant ($p<0.01$); a score between 1.96 and 2.58 is probably significant ($p < 0.05$); a score less than 1.96 is not significant.

Results

54 transfusion-dependent iron overloaded children form the subject of this study. There were 31 boys. 23 were 2 to 5 years of age, 16 were 6 to 9 years and 15 were 10 to 15 years.

27 children had homozygous beta thalassaemia, 5 had Hb E/beta thalassaemia, 14 had congenital dyserythropoietic anaemia, 1 had sideroblastic anaemia and 7 had chronic haemolytic anaemia where no exact diagnosis could be established.

Duration of therapy was 1 to 3 months in 6 patients, 4 to 6 months in 7, 7 to 9 months in 8, and 10 to 12 months in 33. Mean duration of therapy was 9 months.

Efficacy of deferiprone

Initial serum ferritin levels were obtained in all 54 patients and ranged from 1500 to 10 700 ng/ml with a mean of 5743. Subsequent serum ferritin levels were obtained in 48 patients and ranged from 740 to 7300 ng/ml with a mean of 3558. In 47 of the 48 patients subsequent serum ferritin levels were lower than initial levels. Second serum ferritin levels were not available in the 6 patients who received deferiprone therapy for less than 4 months. Correlation between initial serum ferritin level, mean duration of therapy and mean percentage reduction of serum ferritin is shown in Table 1.

The number of patients showing different percentage reductions in the serum ferritin level is shown in Table 2.

Table 1. Correlation between inital serum ferritin level, mean duration of therapy and mean percentage reduction of serum ferritin

Initial serum ferritin (ng/ml)	*Number of patients*	*Mean duration of therapy (SD) (months)*	*Mean % reduction of serum ferritin (SD)*
<5000	16	10 (3)	32 (15)
5000-8000	21	10 (2)	38 (26)
>8000	10	9 (3)	46 (19)

Table 2. Number of patients showing different percentage reductions in the serum ferritin level

% reduction of serum ferritin	*Number of patients*	*Mean duration of therapy in months (SD)*
<20%	11	10 (2)
20-40%	16	11 (1)
>40%	21	9 (3)

Adverse effects

One child developed severe neutropaenia and agranulocytosis (neutrophils < 0.5 x 10^9/1) after 4 months of therapy. Deferiprone was discontinued and the patient was monitored in the ward. The neutrophil count returned to normal within 10 days without any treatment. Deferiprone was not re-started in this patient.

11 children developed arthropathy following deferiprone therapy. There was swelling of the joints (ankle or knee) in 7 patients and arthralgia in 4 patients. The arthropathy developed 3 to 9 months after commencement of deferiprone therapy and responded well to ibuprofen therapy. In 6 patients the dose of deferiprone was reduced to 50 mg/kg/day. Deferiprone was not discontinued in any patient with arthropathy. Thrombocytopaenia was not found in any of the patients. The serum transaminase levels were raised on one or more occasions in 5 patients. In all 5 patients the serum transaminases reverted to pre- treatment levels or lower despite continuation of deferiprone therapy. In one patient deferipone therapy was discontinued after 4 months because of severe neutropaenia. Four others dropped out after receiving therapy for 1 to 3 months.

Discussion

In Sri Lanka there are about 1000 thalassaemic patients of whom only about 10% possess portable electronic pumps to administer subcutaneous desferrioxamine. Most thalassaemic patients receive desferrioxamine only when they come to hospital for their monthly transfusions. Thus, in Sri Lanka, the majority of thalassaemic patients could benefit from deferiprone.

Let us first consider the efficacy of deferiprone. 47 of the 48 patients (98%) who had 2 or more serum ferritin estimations achieved negative iron balance. The mean serum ferritin level declined from 5743 ng/ml to 3558 ng/ml ($Z=5.37$; $P<0.001$) over a mean duration of 9±3 months. Table 1 shows adequate reduction of the serum ferritin level irrespective of the magnitude of the intial serum ferritin level. Table 2 shows that in 21 patients (44%) the reduction of serum ferritin exceeded 40%. Thus the efficacy of deferiprone is established. In a long term trial where serum ferritin was used to evaluate iron loading, patients with most serum ferritin concentrations less than 2500 ng/ml had an estimated cardiac disease free survival of 91% after 15 years, in contrast to patients in whom most serum ferritin concentrations had exceeded 2500 ng/ml, who had an estimated cardiac disease free interval after 15 years of less than 20% (3). It is expected that, in the long term, most of our patients on deferiprone therapy will achieve serum ferritin concentrations less than 2500 ng/ml.

The most important toxic effect of deferiprone is severe neutropaenia or agranulocytosis (10). This has been observed as early as 6 weeks and up to 21 months after initiating therapy with deferiprone in a dose of 50 to 100 mg/kg/day. Rechallenge has invariably led to a second episode of neutropaenia and is not recommended. The mechanism for the neutropaenia or agranulocytosis remains obscure (10). It seems likely that affected patients have an idiosyncratic sensitivity to deferiprone or one of its metabolites. Deferiprone associated neutropaenia or agranulocytosis appears to be fully reversible. In our series one child (1.9%) after 4 months of deferiprone therapy developed severe neutropaenia which spontaneously reverted to normal on cessation of therapy.

The second important adverse effect and the most common clinical problem associated with deferiprone treatment is joint toxicity (11). This consists of musculoskeletal stiffness, joint pain, and in severe cases, joint effusion, occurring within a few weeks of deferiprone therapy. The large joints are usually affected. In most patients the symptoms and signs resolve spontaneously on discontinuation of the drug or following dose reduction. In a minority of patients with severe arthropathy the drug has to be permanently discontinued. The cause of the deferiprone associated arthropathy is not known. It is thought that as iron is shifted into the synovium and incompletely complexed with deferiprone, increased production of free radicals may result in the peroxidation of synovial membranes. In our series 11 children (20%) developed deferiprone related arthropathy, which responded to therapy with ibuprofen, and in some cases, a reduction of the dose.

Fluctuations in liver function during deferiprone therapy were first reported in 1990 (12), and appeared to be more frequent in patients infected with hepatitis C. In all cases the raised transaminase levels gradually settled to pre-treatment levels or lower after 3 months of therapy. In our series the serum transaminases were raised on some occasion in 5 patients (9%) on deferiprone therapy, but reverted to pre-treatment levels or lower despite continuation of therapy. In no patient was there a progressive rise of the transaminase levels. Thus the safety of deferiprone is established.

We conclude that deferiprone is a safe and effective oral iron-chelating agent which can be used, under strict supervision, in transfusion-dependent iron overloaded children.

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Use the best possible word

Knowledge of a language is measured by the nice and exact appreciation of words. There is no more important element in the technique of rhetoric than the continual employment of the best possible word.

Winston Churchill