IRON-CHELATION THERAPY WITH ORAL DEFERIPRONE IN PATIENTS WITH THALASSEMIA MAJOR

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Abstract *Background.* To determine whether the orally active iron chelator deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one) is efficacious in the treatment of iron overload in patients with thalassemia major, we conducted a prospective trial of deferiprone in 21 patients unable or unwilling to use standard chelation therapy with parenteral deferoxamine.

Methods. Hepatic iron stores were determined yearly by chemical analysis of liver-biopsy specimens or magnetic-susceptibility measurements. Detailed clinical and laboratory studies were used to monitor safety and compliance.

Results. The patients received deferiprone therapy for a mean ($\pm$SE) of 3.1 ± 0.3 years. Ten patients in whom previous chelation therapy with deferoxamine had been ineffective had initial hepatic iron concentrations of at least 80 μmol per gram of liver, wet weight — values associated with complications of iron overload. Hepatic iron concentrations decreased in all 10 patients, from 125.3 ± 11.5 to 60.3 ± 9.6 μmol per gram ($P<0.005$), with values that were less than 80 μmol per gram in 8 of the 10 patients ($P<0.005$). In all 11 patients in whom deferoxamine therapy had previously been effective, deferiprone maintained hepatic iron concentrations below 80 μmol of iron per gram.

Conclusions. Oral deferiprone induces sustained decreases in body iron to concentrations compatible with the avoidance of complications from iron overload. The risk of agranulocytosis associated with deferiprone may restrict its administration to patients who are unable or unwilling to use deferoxamine. (N Engl J Med 1995;332: 918-22.)

IN patients with thalassemia major, a regular program of transfusion sustains growth and development during childhood, but without concomitant chelation therapy, iron within the transfused red cells accumulates inexorably.[1] Excess iron damages the liver, endocrine organs, and heart and may be fatal by adolescence.[2] Two recent prospective trials have demonstrated that treatment with deferoxamine B mesylate can prevent the complications of iron overload and improve survival in thalassemia major.[3,4] Both studies showed that the principal determinant of the clinical outcome was the magnitude of the body iron load. In patients able to take sufficient doses of deferoxamine to control the body iron load, the risk of cardiac disease and other complications was low, and survival after 15 years exceeded 90 percent. Conversely, when the body iron load was not controlled, the risk of complications was high, and the probability of survival to the age of 25 years was only about 30 percent.

Some patients are unable or unwilling to receive deferoxamine treatment, because of allergy, toxic effects,[5] an inability to comply with prolonged parenteral infusions, or unavailability of the drug.[1] A possible alternative to deferoxamine, the orally active iron-chelating agent deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one), has undergone preliminary evaluation in the United Kingdom, Canada, Europe, and India.[6-16] Studies using the serum ferritin concentration as an indirect estimate of the body iron load suggest that the drug may be effective, but in some patients treated with deferiprone, reversible neutropenia or agranulocytosis has developed.[14,17,18] This adverse effect emphasizes the need to assess the balance between risk and benefit by directly measuring the efficacy of deferiprone in reducing body iron. We report the results of a prospective study of deferiprone in patients unable or unwilling to use deferoxamine in whom the effect of deferiprone on the body iron burden was assessed with serial direct determinations of hepatic iron concentrations.

METHODS

Patients

Patients with thalassemia major who were unwilling or unable to use deferoxamine and who had completed one or more years of treatment were enrolled in the trial. Each patient received transfusions at three- to four-week intervals to maintain the hemoglobin concentration at a level above 10 g per deciliter (approximately 10 g of transfused iron yearly in a 70-kg adult). Because of toxic effects of deferoxamine (hearing loss[19] or metaphyseal dysplasia[20]), unmanageable local reactions, or infusions of less than 50 percent of the prescribed dose for at least one year, deferoxamine had been administered in doses insufficient to maintain a negative iron balance in some patients. Two patients with insulin-dependent diabetes had cardiac disease requiring medication. Fourteen patients had elevated serum alanine aminotransferase levels (77 ± 14 U per liter [normal value, <40]); 13 had antibodies to hepatitis C. Five patients had previously undergone short-term studies to determine deferiprone-induced urinary and fecal iron excretion.[11]

The study was approved by the Hospital for Sick Children's human-subjects committee and by the Health Protection Branch, Health and Welfare Canada (File No. 9427-H1117-41C). The protocol for the magnetic-susceptibility studies was approved by the Com-

mittee on Human Investigation, MetroHealth Medical Center, Cleveland. Written informed consent was obtained from each patient or a parent of the patient.

Patients were given a total daily dose of 75 mg of deferiprone per kilogram of body weight, to be taken orally every eight hours. Deferiprone was prepared according to published methods[21] and encapsulated by Novopharm Pharmaceuticals, Toronto.

Efficacy

We assessed body iron burden by measuring the hepatic iron concentration, using chemical analysis of tissue obtained by liver biopsy or noninvasive magnetic measurements in vivo. The iron content of biopsy specimens was determined as previously described.[12,22] Magnetic measurements of hepatic iron were performed with a superconducting quantum-interference-device susceptometer (Biomagnetic Technologies, San Diego, Calif.). The ability of this instrument to provide measurements of hepatic iron that are quantitatively equivalent to those obtained by a chemical analysis of tissue has been demonstrated elsewhere.[22] The results of the chemical and magnetic measurements were used interchangeably. Their quantitative equivalence was verified throughout the course of the study by comparisons of paired chemical and magnetic determinations ($n=66$, $r=0.98$, $P<0.001$). Serum ferritin concentrations were measured every two months with a commercial kit (Ramco Laboratories, Houston).

To determine whether deferiprone could maintain body iron concentrations at levels below those associated with complications from iron overload, we used criteria established by two recent prospective trials of deferoxamine in patients with thalassemia.[3,4] In the first trial, chelation therapy was defined as effective if the ratio of the total transfusional iron load to the cumulative use of deferoxamine was less than 0.6 mmol of iron per gram of deferoxamine; chelation therapy was considered ineffective if the ratio was greater than or equal to this value. As detailed previously,[3] a regression analysis indicated that the corresponding concentration of hepatic iron was about 80 μmol of iron per gram of liver, wet weight (normal range, 1 to 9). In the present trial, chelation therapy was considered effective if the hepatic iron concentration was less than 80 μmol per gram, and ineffective if the concentration was 80 μmol per gram or greater.

In the second trial, chelation therapy was considered effective if the value of most serum ferritin measurements was less than 2500 μg per liter, whereas therapy was considered ineffective if the value of most measurements was 2500 μg per liter or greater.[4] We used similar criteria in the present trial.

Safety

Safety was determined by monitoring the patients for abnormalities reported in animal studies.[23-27] Serum alanine aminotransferase, electrolytes, urea nitrogen, creatinine, glucose, cholesterol, triglyceride, albumin, bilirubin, alkaline phosphatase, calcium, phosphate, magnesium, zinc, copper, amylase, and uric acid concentrations and prothrombin time were also monitored regularly.

Compliance

Compliance was assessed with the Medication Event Monitoring System,[28] in which bottles with microprocessors in the caps are used to monitor the frequency of bottle opening. Patients were instructed to supplement a missed dose at the time of the subsequent dose (recorded as a delay but not as noncompliance) but not to supplement more than one missed dose, in order to avoid excessive peak deferiprone concentrations.

Statistical Analysis

Data are presented as means ±SE. Initial and final (most recent) data were compared with Student's t-test for paired data. The Fisher–Irwin exact test was used to determine the proportions of patients in two groups formed with the use of dichotomous variables. The relation between hepatic iron and serum ferritin concentrations was determined with Pearson's coefficient of correlation and a linear regression analysis. The coefficient of determination was used to estimate the proportion of variation in serum ferritin concentrations that could

be accounted for by variation in hepatic iron stores. All tests were two-tailed; a P value of 0.025 was considered to indicate statistical significance.

RESULTS

Twenty-one patients (with a mean age of 22 ± 1.1 years; range, 7.5 to 31) received deferiprone for a mean of 3.1 ± 0.3 years (range, 1 to 4.8), yielding a cumulative total of 756 patient-months (63 patient-years) of observation.

Efficacy

Body Iron Stores

Figure 1 shows the initial and final hepatic iron concentrations in all 21 patients. The mean hepatic iron concentration decreased from 80.7 ± 10.8 to 46.8 ± 5.9 μmol per gram ($P<0.005$). In the 10 patients who had previously received ineffective chelation therapy with deferoxamine, the mean initial hepatic iron concentration was 125.3 ± 11.5 μmol per gram. After a mean of 34.8 ± 3.8 months of treatment with deferiprone, the mean concentration had decreased to 60.3 ± 9.6 μmol per gram ($P<0.005$); in eight patients hepatic iron con-
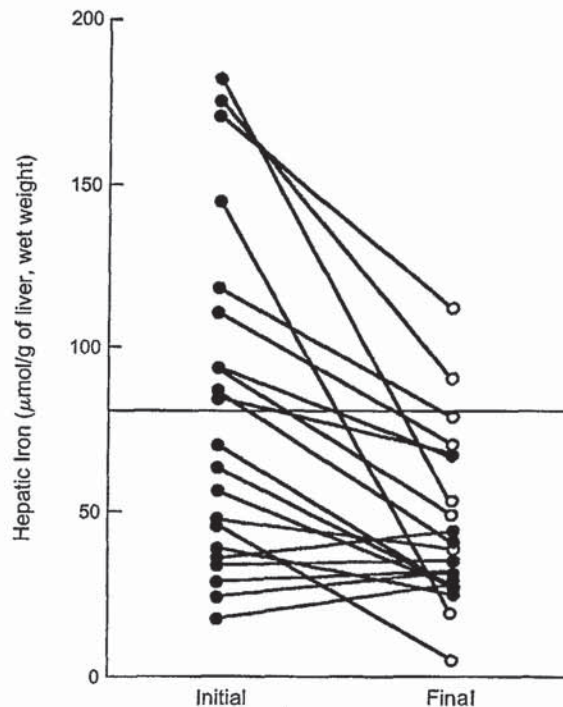

Figure 1. Initial and Final Hepatic Iron Concentrations in 21 Patients with Thalassemia Major Treated with Deferiprone.

The horizontal line indicates the value (80 μmol of iron per gram of liver) below which patients treated with deferoxamine remain free of the complications of iron overload[3] (see text). Solid circles indicate the hepatic iron concentrations determined by chemical analysis of liver-biopsy specimens; open circles indicate the hepatic iron concentrations determined by magnetic-susceptibility studies.

centrations had fallen to a level below 80 μmol per gram (P<0.005). In the 11 patients who had previously received effective chelation therapy with deferoxamine, the mean initial hepatic iron concentration was 43.7±4.8 μmol per gram. After a mean of 37.4±5.4 months of deferoxamine therapy, the mean hepatic iron concentration was 32.5±4.3 μmol per gram (P not significant); the hepatic iron concentration remained below 80 μmol per gram in all 11 patients.

Serum Ferritin Concentrations

Figure 2 shows the initial and final serum ferritin concentrations in the 21 patients. The mean serum ferritin concentration declined from 3975±766 to 2546±381 μg per liter (P<0.005). Among 12 patients with initial serum ferritin concentrations equal to or exceeding 2500 μg per liter (mean, 5759±1077), the mean value decreased progressively to 3273±568 μg per liter (P<0.005) during a mean of 38.5±3.5 months of deferiprone therapy. In 5 of these 12 patients, the final serum ferritin concentrations were less than 2500 μg per liter (P<0.02). Among nine patients with initial values below 2500 μg per liter (mean, 1596±243), the mean serum ferritin concentration had not changed significantly after 33.5±6.2 months (1768±251 μg per liter).

Comparison of Hepatic Iron and Serum Ferritin Concentrations

Figure 3 compares the indirect estimation of body iron, based on the serum ferritin concentration, with the reference method, based on the hepatic iron concentration. The correlation between these measurements was significant (r=0.73, P<0.005).

Safety

Complete blood counts, obtained weekly in all patients, did not change significantly during treatment. Neither the reduction nor the cessation of deferiprone was required because of a change in the blood count in any patient.

Because of reports of deferiprone-induced thymic atrophy in animals,[27] we monitored immune function in the study patients. The results of tests for T-cell subgroups, lymphocyte proliferation, candida, immunoglobulins, specific antibodies (to diphtheria, poliovirus, and measles), isohemagglutinin levels, and complement (C3, C4, and CH_{50}) levels were similar to those in 20 patients treated with deferoxamine (unpublished data).

Annual rheumatologic examinations were performed because of reports of deferiprone-associated arthropathy.[14,15] Joint pain developed in three patients, whose clinical course has been reported elsewhere.[29] Because of one report of deferiprone-associated systemic lupus erythematosus,[30] tests for antinuclear antibodies and rheumatoid factor were performed twice yearly; tests for anti-DNA and antihistone antibodies were performed initially and yearly. No significant changes in
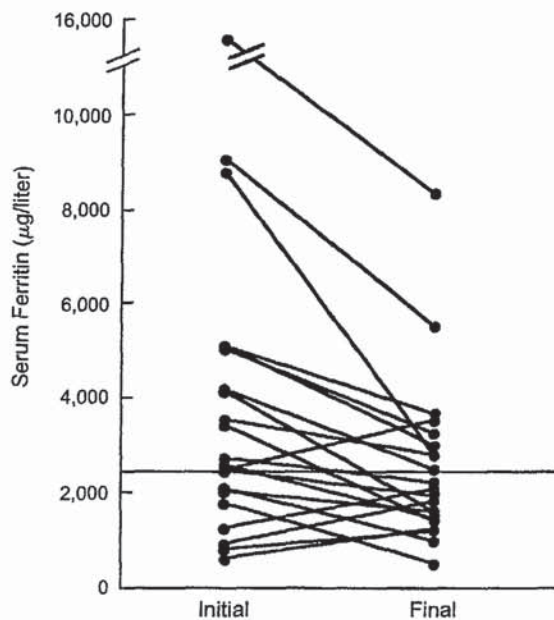

Figure 2. Initial and Final Serum Ferritin Concentrations in 21 Patients with Thalassemia Major Treated with Deferiprone.
The horizontal line indicates the value (2500 μg of ferritin per liter) below which patients treated with deferoxamine remain free of the complications of iron overload[4] (see text).

antinuclear antibodies or rheumatoid factor were noted; anti-DNA and antihistone antibodies were not detected at any time during the study.

Reductions in serum alanine aminotransferase levels were observed in most of the patients, whether or not they had evidence of previous hepatitis C infection. In one patient with a positive test for hepatitis C antibody, fluctuating elevations of alanine aminotransferase levels were probably related to deferiprone treatment, since they declined after the withdrawal of the drug.

The results of adrenal-stimulation tests, performed initially, after one and six months, and yearly thereafter, were normal. Decreases in serum zinc levels[14] were not observed.

Compliance

Data on compliance, determined according to the Medication Event Monitoring System, were available for 19 patients during the last year of deferiprone treatment. The mean compliance rate (percentage of prescribed drug actually taken) was 85±3 percent (range, 41 to 98). The rate of compliance was very high (90±1 percent) among all but three patients; all three had also had a low rate of compliance with deferoxamine therapy. These three patients had high initial hepatic iron concentrations (88, 121, and 178 μmol per gram), which were substantially reduced (by 50, 85, and 36
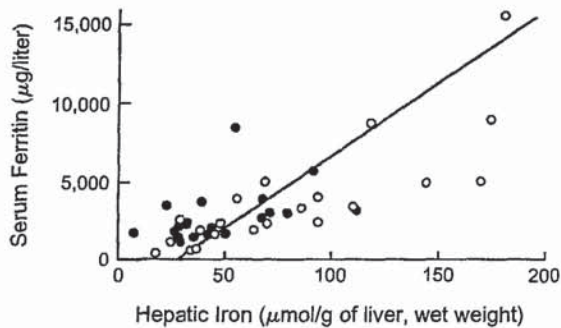
Figure 3. Comparison of Hepatic Iron and Serum Ferritin Concentrations.

Indirect estimation of the body iron load, based on the serum ferritin concentration, is compared with the reference method, based on the direct measurement of hepatic iron levels by chemical analysis or magnetic-susceptibility studies. Open circles denote the values at the start of the trial (before deferiprone therapy), and solid circles the values at the time of the final analysis. The diagonal line denotes the simple linear least-squares regression between the two variables.

percent) with deferiprone therapy, despite compliance rates of only 63, 71, and 41 percent, respectively.

DISCUSSION

Deferoxamine therapy ameliorates hepatic, cardiac, and endocrine dysfunction; improves growth and sexual maturation; and prolongs survival in patients with iron overload.[31-36] Two recent prospective trials of deferoxamine in patients with thalassemia have shown that the magnitude of the body iron burden is the principal determinant of the severity of iron-associated toxicity and of the clinical outcome.[3,4] Thus, the ability of a new iron chelator to reduce body iron stores and maintain them at concentrations associated with a low risk of early death and complications of iron overload is a paramount consideration.

In this trial, we evaluated the efficacy of deferiprone by direct determination of hepatic iron concentrations. In 10 patients in whom deferoxamine had failed to reduce hepatic iron stores to a level below 80 μmol of iron per gram (levels associated with an increased risk of cardiac disease and early death), the body iron load was uniformly reduced with deferiprone (P<0.005). In 8 of the 10 patients, hepatic iron concentrations decreased to less than 80 μmol per gram. In the other two patients, both with high initial hepatic iron concentrations, iron storage was reduced by about 30 and 50 percent after 15 and 39 months of treatment, respectively. In all 11 patients in whom previous deferoxamine therapy had been considered effective, the hepatic iron concentration was maintained at a level below 80 μmol per gram, with no significant change during deferiprone therapy.

With the serum ferritin concentration used as an indirect means of assessing the body iron burden, the

findings were similar, although the classification of patients according to the efficacy of previous therapy differed somewhat. In all 12 patients with initial serum ferritin concentrations equal to or exceeding 2500 μg per liter (the criterion for previously ineffective chelation therapy), deferiprone induced reductions in serum ferritin concentrations. During a mean period of 38.5±3.5 months, the mean serum ferritin concentration in these patients declined from 5759±1077 to 3273±568 μg per liter (P<0.005). Among the nine patients with initial serum ferritin concentrations below 2500 μg per liter, the mean concentration did not change significantly. These data demonstrate that deferiprone can both reduce and maintain body iron at concentrations associated with a low risk of iron-related complications.

In patients with a history of effective chelation therapy, deferiprone did not reduce body iron to a level below that achieved previously with deferoxamine. This observation is consistent with the finding that the daily dose of deferiprone used in our study (75 mg per kilogram of body weight) induces less iron excretion than the standard daily dose of deferoxamine (50 mg per kilogram).[11,16] Nonetheless, deferiprone reduced body iron concentrations in all our patients with a history of ineffective chelation therapy with deferoxamine. Improved compliance almost certainly explains this apparent anomaly. Deferoxamine is the more efficient chelating agent, but the difficulty of compliance with parenteral administration limits the drug's effectiveness.[36] In this study, a high rate of compliance improved the long-term effectiveness of chelation therapy with deferiprone, even in patients who had not been able to use deferoxamine successfully.

The differences in the direct and indirect means of evaluating deferiprone therapy are apparent from the data in Figure 3. These data show that a reliance on the serum ferritin concentration alone can lead to an inaccurate assessment of the body iron load in individual patients, in part because the serum ferritin concentration is influenced not only by body iron but also by ineffective erythropoiesis, ascorbate deficiency, liver disease, and other conditions that are common in patients with thalassemia.[37]

We used a hepatic iron concentration under 80 μmol per gram and a serum ferritin concentration under 2500 μg per liter as the criteria for effective chelation therapy to facilitate the comparison between deferiprone and deferoxamine. These values may not represent the optimal goals for the treatment of iron overload. They are derived from prospective trials lasting more than a decade,[3,4] but 10 years is still too short a period for the evaluation of lifelong therapy. The optimal level of body iron, which remains to be determined, may be considerably lower than that reflected by these values.

The adverse effects of deferiprone included joint pain in one patient[29] and a reversible elevation in the

serum alanine aminotransferase level in another. Although not observed in our patients, severe neutropenia or agranulocytosis has been reported in 11 patients worldwide (Hoffbrand AV: personal communication). This toxic effect has been transient in all patients to date, but the possibility of its occurrence mandates regular monitoring of neutrophil counts during treatment with deferiprone. The incidence of agranulocytosis is being determined in a prospective multicenter trial in Canada, Italy, and the United States, under corporate sponsorship (Apotex Research, Toronto) and approved by the Canadian Health Protection Branch, the Italian Ministry of Health, and the U.S. Food and Drug Administration. The results of this study should determine the commercial availability of deferiprone. The costs associated with its administration, although likely to be less than those associated with parenteral administration of deferoxamine, have not yet been determined.

Our data provide direct evidence of the efficacy of deferiprone for the treatment of iron overload in patients with thalassemia major. Deferiprone decreases body iron concentrations and maintains them at levels below those associated with the complications of iron overload. Nevertheless, until the risk of agranulocytosis is determined, deferiprone should be considered as an investigational drug for patients unable or unwilling to use parenteral deferoxamine.

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