

# Complications of Combined Treatment with Deferiprone and Desferrioxamine in Thalassemic Patients

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## Abstract

Although successful iron chelation with deferiprone is associated with significant complications, patient's compliance with medication regimens is of a high priority. The present study did evaluate the complications and compliance of domestically-manufactured deferiprone combined with desferrioxamine for iron chelation therapy. A total of 32 major beta thalassemic patients with cardiomyopathy were enrolled in the study and were monitored clinically and paraclinically. Upon every visit, the patients were prescribed only the number of tablets deemed necessary. The side effects observed as nausea (25%), vomiting (12%), neutropenia (12%), thrombocytopenia (6%), and joint pain (3%) without agranulocytosis or increased liver enzymes to more than twice the normal values. Deferiprone was discontinued in 30% of patients because of severe refractory gastrointestinal complaints (12%), recurrent neutropenia (6%), recurrent thrombocytopenia (6%), severe arthropathy (3%), or interferon therapy (3%). None of the patients, except one, remembered taking full number of the prescribed tablets. Twenty seven patients used 35% to 92% of the prescribed tablets. Poor compliance with deferiprone due to patient's neglect to take the drug 3 times a day for a prolonged period was the main problem in this regimen. Although thrombocytopenia was more common compared with those of previous reports, other complications were seen with equal or lower frequencies. This study shows that a lower daily dose is the most favorable property of an oral iron chelator for prolonged usage.

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**Keywords** • Deferiprone • thalassemia • compliance

## Introduction

**E**ffective and conventional iron chelation is the main strategy for the management of major thalassemia. However, chelation with desferrioxamine may be inadequate for several reasons.<sup>1,2</sup> It has been estimated that desferrioxamine is prescribed for 25,000 out of 72,000 patients with major thalassemia who are regularly transfused.<sup>1</sup> Despite the wide availability of desferrioxamine in western countries, some patients are unable to comply sufficiently with prescribed treatments because of the unpleasant and cumbersome nature of effective chelation regimens, which require prolonged and daily subcutaneous or intravenous desferrioxamine administration.<sup>2</sup> Furthermore, some patients develop side effects with variable severity that affect compliance or in extreme cases result

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in the cessation of treatment. Therefore, it is not surprising that some of such patients continue to develop iron-induced complications or die from iron-induced cardiac disease.

New chelators, particularly those that are administered orally, are expected to have a major impact on the management of patients with thalassemia. A choice of more than one chelator would permit a flexible approach to chelation therapy, and could possibly improve compliance with treatment and overall quality of life. Chelators with distinct chemical properties may have different iron carrying capacities and accessibilities to different iron pools. To explain these effects, it has been proposed that a bidentate or tridentate ligand, with access to a variety of tissues acts as a "shuttle" to mobilize iron from tissue compartments to the bloodstream, where the chelator may exchange iron with a larger hexadentate.<sup>3,4</sup> Mourad and colleagues reported that giving deferiprone everyday and desferrioxamine twice a week produced iron excretion comparable to that achieved with desferrioxamine administered 5 days a week.<sup>5</sup> This regimen of chelation is more tolerable, and may be more attractive for patients who are unable to comply with regular daily use of desferrioxamine. Since some of the toxic effects of the chelators are dose-dependent, combined treatment may make it possible to reduce the dose of one or both drugs, hence reducing their toxicity while maintaining their effective chelation.<sup>6-9</sup>

Although, unexpected side effects have not been consistently observed in patients receiving combined treatment with desferrioxamine and deferiprone, prospective randomized studies are needed to establish the risks and benefits of this approach. This is important, especially in the countries where a national brand of iron chelators is manufactured and prescribed for patients. The objective of the present study was to examine the safety and tolerability of combined iron chelation therapy in patients with major beta thalassemia who lived in Sistan and Baluchestan province, southeast Iran.

## Patients and Methods

### Patients

Transfusion-dependent thalassemic patients (n=32) older than 8 years, with symptomatic cardiomyopathy, were considered for combined iron chelation therapy with desferrioxamine and deferiprone in the Thalassemia Clinic of Zahedan, Sistan and Baluchestan, Iran from October 2003 to September 2005. All patients were homozygotes for beta-thalassemia, and used to receive regular packed red cell transfusions every 2 to 3

weeks and subcutaneous infusions of desferrioxamine (40-50 mg/kg) 5-6 nights a week. They used to have a good compliance index of more than 60% in the past 3 years. The patients refused intensive intravenous chelation despite extensive advice on the importance of chelation. Criteria for exclusion from the study were pregnancy or lactation, previous serious adverse side effects with desferrioxamine or deferiprone, a history of neutropenia, positive antinuclear antibody, interferon therapy for hepatitis C virus (HCV), and serologic evidence of human immunodeficiency virus.

The study was approved by the Ethics Committee, Zahedan University of Medical Sciences. The patients were given a full explanation of the procedure, the risks as well as consequences of neutropenia and agranulocytosis, and a written consent was obtained from the participants.

### Methods

All participants were advised for weekly monitoring of complete blood count (CBC). White cell differential counts and CBC were obtained using an electronic cell counter (Sis-max Coulter). If the neutrophil count was below 1500/ml, deferiprone would temporarily be interrupted and CBC would be repeated every 2 to 3 days. Deferiprone would be discontinued if neutropenia persisted for 7 to 10 days, recurred, or were below 500/ml. The treatment with deferiprone was also ceased in patients whose platelet counts were above 100,000/ml prior to the study, but fell below 50,000/ml and persisted during the study.

Using standard methods, the levels of liver enzymes Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were determined every 3 months. Plasma zinc levels could not be checked for all patients before and after the study. Serum ferritin levels were measured using venous blood every 3 to 6 months with an automated immunoassay system. A pediatric cardiologist monitored the cardiac functions once or twice a year or on-demand. Adverse events and compliance were checked on each transfusion visit.

Chelation treatment was tailored to the needs of the individual patients. Deferiprone (Avicenna Laboratories, Iran) was prescribed at a dose of 75 mg/kg/day in three divided oral administrations. Desferrioxamine (Desferal®, Novartis, Austria) was given subcutaneously at 30-40 mg/kg/day over 8-10 hours/day for 2 to 3 days/week according to the ferritin level. This comprised 3 days a week when the ferritin was more than 3000 ng/ml, and 2 days a week when its level was 2000-3000 ng/ml. The patients received the number of tablets and vials

needed for their next course. If a patient failed to take the medications, he or she would be asked about the reasons, and reminded of the importance of continuing an uninterrupted schedule of the medication. The total numbers of tablets required and used by the patients were compared at the end of the study.

#### Statistical analysis

The data were described or analyzed using descriptive or analytical statistics. Paired *t* test was used to analyze the changes in the levels of serum ferritin, as well as AST and ALT levels, by SPSS software (version 11). A  $P \leq 0.05$  was considered statistically significant.

### Results

A total of 18 males and 14 females, with a mean age of 18.4 years enrolled in the study. The Mean duration of drug exposure was  $20.1 \pm 1.4$  months per patient. Eight patients (25%) experienced nausea most frequently during the first week of combination therapy. Nausea associated with vomiting or abdominal pain was observed in four patients (12%). These patients discontinued the treatment after 4 to 21 months because of refractory cumbersome symptoms regardless of various medical interventions.

Serum AST and ALT were normal prior to treatment in 15 and 11 subjects, respectively. In patients who had high serum AST and ALT levels at the beginning of the study, AST and ALT decreased by 20% in 12 out of 17 cases (71%) and 12 out of 21 cases (57%), respectively. Although serum AST and ALT levels increased more than 20% in 14% and 22% of patients respectively at the end of study, they did not increase to more than twice the normal values. Serum levels of ALT ( $81.7 \pm 13.3$  U/l) and AST ( $59.1 \pm 6.5$  U/l) during the treatment were not significantly different from the baseline levels of ALT ( $74.2 \pm 12.9$  U/l) and AST ( $53.3 \pm 8.4$  U/l), respectively. Although 3 patients were HCV-positive (HCV RNA), only in one case deferiprone was discontinued because of the necessity for treatment with interferon.

Two patients (6.25%) developed joint problems. One patient with serum ferritin above 4,000 ng/ml developed bilateral painful knee swelling as well as pain in the hand joints after a few weeks of combined treatment. Symptoms and signs were not diminished by increasing the desferrioxamine infusion days from 2 days to 7 days per week but disappeared when deferiprone was discontinued after 4<sup>th</sup> month of treatment.

Two patients developed persistent or recurrent neutropenia with absolute neutrophil count

between 500/ml and 1500/ml during 23-25 months of combined treatment. Another 2 cases developed recurrent thrombocytopenia ( $< 50,000$ /ml), which disappeared immediately after stopping deferiprone, and recurred upon resuming the drug administration. Two patients developed an episode of transient neutropenia after 25-27 months. Agranulocytosis (500/ml) was not observed in any patient. However, four patients who developed recurrent neutropenia or thrombocytopenia were HCV-negative, and had not undergone splenectomy. We did not use granulocyte colony-stimulating factor for such four cases and discontinued deferiprone.

Of the 32 patients, 12 dropped out of the study after 2-27 months. Three cases died between 4-25 months because of severe cardiac problems, which had been diagnosed prior to the study. Nine patients (28%) withdrew because of adverse events, including neutropenia ( $n=2$ ), thrombocytopenia ( $n=2$ ), gastrointestinal problems ( $n=4$ ), and arthropathy ( $n=1$ ). In addition, one patient withdrew from the study because of interferon-induced neutropenia. Deferiprone administration was not discontinued if patients did not come for weekly monitoring of their CBC and had already accepted, in writing, the risks of combination therapy in iron induced cardiomyopathy.

Out of the 27 patients, 25 were treated for more than one year. During this period the total numbers of deferiprone required for the patients, as prescribed by the physician, were charted. Also, the numbers of tablets consumed during one year, as declared by the patients, were recorded in each case. However, in two cases because of missing data such a recording was not possible. The compliance index (CI), expressed for each patient as the ratio of the number of used tablet/number of prescribed tablets  $\times 100$ , was  $62 \pm 16\%$ . There was a significant reduction in the level of Ferritin (from  $3179 \pm 1599$  ng/ml to  $2408.3 \pm 1616$  ng/ml) during the combined treatment.

### Discussion

The findings of the present study suggest that gastrointestinal symptoms were the most frequent side effects. They also showed that the side effects were so severe and refractory to medical interventions, which led to deferiprone discontinuation. This finding is similar to a previous report.<sup>10</sup> The severity of the symptoms might have been due to variations in the synthesis of the Iranian dosage form of deferiprone used in the present study.

The study also showed that serum levels of ALT and AST did decrease, although not significantly, which were not associated with liver

dysfunction. This was similar to a large trial,<sup>5</sup> in which mean ALT levels did not increase among 151 patients treated for 3 years,<sup>5</sup> but was in contrast to another trial,<sup>10-12</sup> in which some patients were withdrawn from the study because of raised ALT levels. The decrease of the enzymes might have been due to a more efficient chelation and subsequent reduction of liver cytolysis.<sup>11</sup>

The study also showed that joint problems during combined treatment appeared to occur less frequently than with the use of deferiprone alone, which suggested a possible decrease in the intra-articular labile iron pool.<sup>10,13-15</sup> The incidence of agranulocytosis was nil in the present study, which was similar to a previous study conducted in a multicenter setting involving 187 patients on long-term treatment with deferiprone alone.<sup>13</sup> Studies with larger numbers of patients are required to clarify whether combined treatment is associated with a higher or lower incidence of agranulocytosis compared with monotherapy with deferiprone. However, the incidence of neutropenia was more frequent in our patients than that reported earlier.<sup>10</sup>

This study showed that combination therapy was associated with thrombocytopenia in 6% of patients. The effect of combination therapy on thrombocytes has not been reported previously. However, it was reported to occur in 20 out of 44 patients under the age of 6 years after 3 months to 1 year of deferiprone therapy.<sup>16</sup> It was also reported that deferiprone therapy had to stop in one case because of thrombocytopenia.<sup>17</sup> Careful monitoring of blood count, a critical aspect in the follow-up of patients, is essential for patients receiving combination therapy.

Prior to this study, our patients had shown good compliance to desferrioxamine by using more than 60% of the prescribed dose within the previous 3 years.<sup>18</sup> The mean patients' compliance to deferiprone was 62.8%, which was lower than expected from an oral formulation when compared with desferrioxamine. There is no report of patients' compliance to deferiprone yet. The fairly low patients' compliance to deferiprone was due to their failure to remember taking their scheduled treatment (3 times daily) for a prolonged period. This problem continued despite repeated and extensive advice on the importance of chelation. By itself, the low compliance might be a very important problem during prolonged deferiprone treatment. Compliance to iron chelation seems to be related not only to the route of administration, but also to the number of treatments per day. Continuous supervision of patients is, thus, of critical importance for achieving an efficient iron chelation especially in low socioeconomic

regions. Regular follow ups and charting compliance index for both deferiprone and desferrioxamine are, therefore, suggested.

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