Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia


Summary

Background Despite the introduction of the parenteral iron chelator desferrioxamine more than 30 years ago, 50% of patients with thalassaemia major die before the age of 35 years, predominantly from iron-induced heart failure. The only alternative treatment is oral deferiprone, but its long-term efficacy on myocardial iron concentrations is unknown.

Methods We compared myocardial iron content and cardiac function in 15 patients receiving long-term deferiprone treatment with 30 matched thalassaemia major controls who were on long-term treatment with desferrioxamine. Myocardial iron concentrations were measured by a new magnetic-resonance T2* technique, which shows values inversely related to tissue iron concentration.

Findings The deferiprone group had significantly less myocardial iron (median 34.0 ms vs 11.4 ms, p=0.02) and higher ejection fractions (mean 70% [SD 6.5%] vs 63% [6.9%], p=0.004) than the desferrioxamine controls. Excess myocardial iron (T2* <20 ms) was less common in the deferiprone controls (four [27%] vs 20 [67%], p=0.025), as was severe (T2* <10 ms) iron overload (one [7%] vs 11 [37%], p=0.04). The odds ratio for excess myocardial iron in the desferrioxamine controls versus the deferiprone group was 5.5 (95% CI 1.2–28.8).

Interpretation Conventional chelation treatment with subcutaneous desferrioxamine does not prevent excess cardiac iron deposition in two-thirds of patients with thalassaemia major, placing them at risk of heart failure and its complications. Oral deferiprone is more effective than desferrioxamine in removal of myocardial iron.

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Introduction

Heart failure due to iron overload can develop either as a result of excess dietary absorption (hereditary haemochromatosis) or from repeated blood transfusions. The most striking model of cardiac iron overload is seen in thalassaemia major, in which heart failure remains the major cause of death (60%), greatly exceeding deaths from infection (13%) and liver disease (6%).1 Despite the introduction of the iron-chelating agent desferrioxamine more than 30 years ago in the UK, 50% of patients still die before reaching the age of 35 years.2 This high mortality is partly the result of difficulties with administration of desferrioxamine. This drug requires long subcutaneous or intravenous infusions on at least 4 days a week; compliance with treatment is inadequate in many cases. The need for an effective alternative approach with an oral iron chelator has long been acknowledged,3 and medium-term results from prospective trials of the oral chelator deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one) seemed promising;4–6 however, the long-term effectiveness of this drug has been questioned because liver iron content is high in some patients.7,8 Since the primary objective of iron-chelation therapy is to prevent the lethal cardiac complications from myocardial iron deposition, myocardial iron and ventricular function should also be taken into account in assessment of the effectiveness of chelating agents. New magnetic resonance techniques can assess both myocardial iron and ventricular function in the same study.9 Our aim, therefore, was to investigate whether deferiprone is effective in controlling myocardial iron.

Methods

Participants We included all patients based at the Whittington Hospital, London, UK, who received chelation with deferiprone alone for longer than 3 years (mean duration 5.7 years [SD 1.8]), between May, 1999, and December, 2000. For each deferiprone patient, we assigned two controls with thalassaemia major, matched for age, sex, and current ferritin concentration, who were receiving standard subcutaneous desferrioxamine. Controls were chosen from the thalassaemic population also treated at this centre. The criteria for matching were a maximum age difference of 5 years (mean difference 2.4 years) and a maximum ferritin difference of 1000 μg/L (mean difference 447 μg/L). When more than two controls were identified, those with the smallest age differences were chosen. All patients received transfusions every 2–3 weeks to maintain the pretransfusion haemoglobin concentration at 90–95 g/L, and all had received iron-chelation therapy since the late 1970s or from early childhood in patients born after this time. Exclusion criteria were the inability to undergo magnetic-resonance scanning (claustrophobia, pregnancy, or pacemaker fitted). The reason for starting deferiprone was refusal or inability to comply with the...
To quantify iron loading in the heart and the liver (figure 1), we measured T2*, a magnetic-resonance variable that is inversely related to tissue iron concentration, by a previously validated method. The technique has high reproducibility both in the liver (coefficient of variation 3-5%) and in the heart (5-0%). All patients were scanned, using the same sequence, with a Picker 1·5 T Edge Scanner (Marconi Medical Systems, Cleveland, OH, USA). Each scan included the measurement of liver and heart iron by means of T2*. For the calculation of liver T2* a single transverse slice through the liver was acquired at nine separate echo times. After subtraction of background noise, the signal intensity of the liver or myocardial parenchyma was plotted against the echo time for the image. A trendline was fitted to the resulting exponential decay curve, with an equation of the form \( y = Ke^{kt - T2^*} \) (where \( K \) is a constant, \( T^E \) the echo time, and \( y \) the signal intensity). Myocardial T2* values measured in healthy volunteers showed a normal distribution with a mean value of 52 ms and a lower 95% confidence limit of 20 ms. We measured ventricular volumes, mass, and ejection fraction by standard cardiovascular magnetic-resonance techniques, which are highly reproducible, with published normal ranges.

Serum ferritin was measured by enzyme immunoassay, and all values are referable to the WHO Ferritin 80/602 First International Standard (normal range 15–300 \( \mu \)g/L).

Follow-up echocardiographic data in the form of M-mode left-ventricular dimensions and shortening fraction (defined as the difference between left-ventricular end-diastolic and end-systolic dimensions as a percentage of end-diastolic dimension) were available for nine of 15 patients who received deferiprone and 20 of 30 desferrioxamine controls. These echocardiograms were taken for clinical reasons for annual or biannual review.

### Statistical analysis

We compared patients' characteristics by means of Student's \( t \) test (age and serum ferritin) or Fisher's exact test (presence or absence of diabetes mellitus, hypopituitarism, hypothyroidism, hepatitis C). Myocardial T2* and liver iron values were positively skewed in all groups, and non-parametric analyses were used for comparison of these variables. Paired comparisons were made between the deferiprone and desferrioxamine groups with each deferiprone patient paired to the mean value of the two matched desferrioxamine patients. Wilcoxon's signed-rank test was used for myocardial T2* and liver iron concentrations, and Student's \( t \) test for indices of left-ventricular function. Since left-ventricular volumes and mass vary with the height and weight of a patient, we normalised these indices to body surface area. We assessed comparisons of proportions of patients with excess myocardial iron deposition in the groups with Fisher's exact test. Unpaired comparisons between the 30 deferiprone control patients and a larger population of 160 patients receiving subcutaneous desferrioxamine were made with the Mann-Whitney \( U \) test (myocardial T2* and liver iron) and the unpaired Student’s \( t \) test (age, left-ventricular ejection fraction, and serum ferritin). The odds ratio for the prevalence of excess myocardial iron in the deferiprone group compared with the desferrioxamine group was calculated with a 95% CI.

### Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
Results

Clinically relevant characteristics for patients in the two study groups are compared in table 1.

The deferiprone-treated group had significantly less myocardial iron than the desferrioxamine-treated group (median myocardial T2* 34·0 vs 11·4 ms, p=0·02, table 2). The deferiprone group also had a higher mean left-ventricular ejection fraction (p=0·004) and less left-ventricular dilatation in systole (p=0·03) and diastole (p=0·01) than the control group. The left-ventricular mass index was lower, but not significantly so, in the deferiprone patients (p=0·09). Excess myocardial iron (myocardial T2* >20 ms) was noted in four (27%) deferiprone-treated patients (p=0·025) and severe iron overload (T2* <10 ms) was seen in one (7%) and 11 (37%), respectively (p=0·04). The odds ratio for excess myocardial iron in the deferiprone-treated patients (n=30) population vs the deferiprone group was 5·5 (95% CI 1·2–28·8).

Liver T2* measurements were converted into dry-weight liver iron measurements as previously described. Despite the lower myocardial iron and improved left-ventricular function in the deferiprone-treated patients (table 2), this group had significantly higher liver iron content than did the desferrioxamine group (median 5·1 vs 3·5 mg/g liver dry weight, p=0·03).

To ensure that the myocardial iron and ventricular function in the desferrioxamine group were representative of these features in the wider population with thalassaemia major, we also compared the results of the desferrioxamine control group with those of a further 160 patients receiving standard subcutaneous treatment with desferrioxamine. The two sets of desferrioxamine-treated patients were similar in age, and there was no significant difference in myocardial iron or left-ventricular ejection fraction, although serum ferritin was higher in the large group (table 3). The proportion of patients with excess myocardial iron deposition (T2* <20 ms) was similar in the two desferrioxamine groups, as was the proportion with severe iron overload.

The median follow-up times with echocardiography in the deferiprone (nine patients) and desferrioxamine (20 patients) groups were 2·5 years (range 1·1–5·9) and 2·1 years (1·4–6·6). The initial and final shortening fractions in the deferiprone group were 33% (SD 9) and 36% (6); the mean improvement was 3·1% (p=0·1), with great improvement seen in two patients (figure 2). The initial and final shortening fractions in the desferrioxamine group were 32% (7) and 33% (5); the mean improvement was 0·7% (p=0·6) (figure 3). Although there was no significant difference in end-systolic dimensions between the groups at the initial scan (deferiprone patients 3·4 cm, desferrioxamine patients 3·5 cm, p=0·4), end-systolic dimensions were significantly smaller in the deferiprone group at the final scan (3·1 vs 3·6 cm, p=0·02).

Table 2: Paired comparisons of heart and liver iron content and indices of left-ventricular function

Table 3: Comparison of the desferrioxamine control group with a larger population of patients with thalassaemia major treated with subcutaneous desferrioxamine

![Figure 2: M-mode echocardiography in patients treated with deferiprone](image-url)
of low hepatic iron, so the risk of side-effects could be overloads. The disadvantages include high cost, and systemic toxic effects, which include visual and auditory neurotoxic effects, skeletal abnormalities, and growth retardation. Toxicity is increased in the presence of low hepatic iron, so the risk of side-effects could be lessened by reducing the dose when hepatic iron concentrations are low; however, patients should be regularly monitored for such adverse effects. Despite the administration of this arduous regimen for more than 20 years, or from early childhood in younger patients, iron-induced heart failure remains the principal cause of premature death in these patients.

To date, only deferiprone has been introduced for clinical use as an orally active alternative to desferrioxamine. Deferiprone is a bidentate chelator, binding iron in a ratio of three to one, whereas desferrioxamine is a larger hexadentate molecule, binding iron in a one-to-one ratio. Side-effects of deferiprone include discoloured urine (40%), nausea (24%), arthropathy (11%), and reversible agranulocytosis (0-5%). Although results of formal dose-response studies have shown that iron excretion is worse with deferiprone than with desferrioxamine, findings of medium-term clinical trials have shown that it is effective, possibly because compliance is better. However, in a longer trial of 18 patients over 4-6 years, eight patients had hepatic iron concentrations above 80 μmol/g liver wet weight (a value previously believed to be associated with increased risk of cardiac disease, and about equivalent to 15 mg/g dry weight). The investigators concluded that deferiprone "does not adequately control body iron burden". This conclusion is, however, arguable. First, all patients had previously been treated with desferrioxamine, yet ten had hepatic iron concentrations of more than 80 μmol/g liver wet weight at the beginning of the trial. Second, during treatment with deferiprone, the mean liver iron content fell from a mean of 88.7 μmol/g (SD 12.1) to 65.5 μmol/g (7.9) liver wet weight. Third, myocardial iron content was not measured. We aimed to assess the effect of deferiprone on myocardial iron, because heart failure is the main cause of death in thalassaemia, greatly exceeding deaths from liver disease. Thus, the primary role of iron-chelation therapy is to prevent premature death from myocardial iron overload.

The emergence of advanced magnetic-resonance techniques has made possible accurate assessment of both liver and cardiac iron in the same study. Such measurements have shown that myocardial iron cannot be predicted from liver iron concentration, and that left-ventricular ejection fraction is unrelated to liver iron or serum ferritin concentrations in thalassaemic patients. Thus, direct myocardial iron measurements are essential. Our results indicate significantly lower myocardial iron content and a lower proportion of patients with excess myocardial iron in the deferiprone group than in the desferrioxamine controls, combined with better left-ventricular ejection fractions. These findings suggest a cardioprotective effect of deferiprone, arising despite the higher liver iron contents in the deferiprone group. These results show that deferiprone is an effective chelator for myocardial iron, and emphasise the importance of the variation between organs in iron concentrations and most notably the poor correlation between liver and myocardial iron. A possible mechanism for better cardioprotection from deferiprone than from desferrioxamine is its greater ability to penetrate myocardial cells, where excess iron is stored in lysosomes as ferritin and haemosiderin. Deferiprone can cross cell membranes more effectively than desferrioxamine because it is of lower molecular weight and is lipophilic. Conversely, in the liver, desferrioxamine has the advantage of facilitated transport into cells via an active uptake mechanism. Although our results indicate better myocardial iron concentrations with deferiprone and better hepatic iron concentrations with desferrioxamine, there is much variability among patients that remains to be explained. An individualised approach to iron-chelation therapy, with assessment of iron in each target organ might, therefore, be necessary to optimise care of patients.

Our study had some limitations. The retrospective analysis used a magnetic-resonance technique that was not available when treatment with deferiprone was instituted. Ideally, the controls would be matched for baseline myocardial iron deposition, but this information was not available for either group. Although all our patients on long-term deferiprone were included, the
Modell B, Khan M, Darlison M. Survival in beta thalassaemia major.

References

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References


