

ORAL IRON CHELATION THERAPY

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Introduction

Since the introduction of regular subcutaneous infusions of desferrioxamine (DFX) in 1976, the life expectancy of patients with thalassaemia major (TM) and other transfusion-dependent patients with refractory anaemias has substantially improved. Iron from transfused blood accumulates in these patients at an approximate rate daily of 0.5mg/kg body weight. In the absence of chelation therapy, death occurs usually from cardiac failure or arrhythmia. Iron-induced hepatic and endocrine dysfunction, like cardiac disease, can be prevented by adequate chelation with DFX ⁽¹⁾. Moreover, in some patients intensive chelation with DFX given intravenously has reversed cardiac dysfunction. A recent technical advance in the administration of DFX has been the use of constant rate infusers prefilled with DFX. These infusers obviate the need for a battery-operated infusion pump and for the patient to dissolve the drug into solution from powder. They facilitate continuous infusion over 24–48 hours or longer subcutaneously or intravenously. This avoids the accumulation of toxic “free”, non-transferrin bound iron (NTBI), which occurs in plasma in heavily iron-overloaded patients between intermittent subcutaneous infusions.

Although DFX is an effective and safe drug, it is not available to most patients in the world because it is too expensive. Moreover, some patients are sensitive to DFX while others fail to comply with the difficult regime of regularly self-administering the drug subcutaneously. A final reason why DFX may not be available to certain patients is its toxicity. DFX, especially when used in high doses in patients who are not grossly iron loaded, can cause toxicity to the retina, the auditory system, bone, cartilage formation and growth. Because of these problems with the use of DFX, there is a need for a safe, cheap, orally active iron chelator.

Hundreds of compounds have been screened in tissue culture and in animal models, and several have undergone short-term trials in humans.^(2,3) Only one, 1-2 dimethyl-3-hydroxypyridine 4-one (L1, CP20, deferiprone), has survived these short-term trials of efficacy and toxicity and entered long-term clinical trials, lasting in some cases for six years or more. Recent reviews of these clinical trials have been published,^(4,5) and a recent issue of *Acta Haematologica* contains 10 excellent articles dealing with different aspects of iron chelation therapy.⁽⁶⁾

Deferiprone (L1 1,2 Dimethyl-3-Hydroxypyrid-4-One, CP20)

Pharmacology

Deferiprone is rapidly absorbed, but whether from the stomach or upper small intestine or both remains to be established. It appears in plasma with a mean absorption $T^{1/2}$ estimated as 7.1 minutes in one study and 22 minutes in another.⁽⁷⁻⁹⁾ The drug is metabolised to a glucuronide that is incapable of binding iron. Free and iron-bound deferiprone are rapidly cleared from plasma with a $T^{1/2}$ of about 90 minutes; the

glucuronide derivative is excreted more slowly, with a mean plasma $T^{1/2}$ estimated as 148 minutes. Following a single oral dose, only a small fraction of the total drug is found in plasma after 12 hours, 1.3% for deferiprone, 5.3% for the glucuronide. Clearance of the glucuronide is slower in patients with impaired renal function. The drug is excreted in urine free or as its iron or glucuronide derivatives with traces bound to zinc or aluminium. About 80% of a single oral dose appears in urine within the first 24 hours. Whether the remainder is excreted more slowly in the urine is uncertain. Different studies have shown a mean faecal excretion of between zero and 33% of a single oral dose of the drug. Deferiprone probably induces less faecal iron excretion than DFX. It has been estimated to be between 0 and 6mg in one study⁽¹⁰⁾ and 0 in another in patients receiving 75–100mg/kg/day of the drug. The efficacy of the drug, assessed as the proportion of the total oral dose that appears in the urine bound to iron, in the first 24 hours in iron loaded patients is about 4%. No evidence for more rapid clearance or glucuronidation of the drug has been found in long-term deferiprone-treated patients compared to untreated patients, suggesting that deferiprone does not induce its own metabolism. Deferiprone radioactively labelled accumulates mostly in the liver, both in iron-loaded and normal rats, whether the drug is given orally, intraperitoneally or intravenously.⁽¹²⁾ No excessive accumulation in any other organ—including the brain, bone marrow, endocrine organs, heart or thymus—could be demonstrated, except for the gastrointestinal tract and kidneys, which are routes of excretion of deferiprone. Unlike DFX, deferiprone can remove iron from transferrin; it has been estimated that as much as 20% of the iron excreted in the urine in heavily iron-loaded patients given a single dose of deferiprone may be derived from iron bound to transferrin.

Clinical Studies

Initial short-term studies showed that deferiprone 100mg/kg body weight induced urine iron excretion in iron-loaded patients approximately equivalent to that induced by a 12-hour subcutaneous infusion of 50mg/kg DFX.⁽¹³⁻¹⁵⁾ Deferiprone is a bidentate chelator (M.W.139) so three molecules are needed to chelate one atom of iron, whereas DFX is hexadentate and chelates iron one molecule to one atom. Iron excretion is greater in the more iron loaded patients and with larger doses of deferiprone. If the total daily dose of drug is given as two or three subdoses throughout the 24 hours, there is usually increased excretion compared with a single large dose. There is, however, no consistent difference in iron excretion whether the drug is taken fasting, with food, or with additional oral vitamin C.

The most widely used regime in long-term clinical trials is 25 mg/kg given three times daily. Whereas it is difficult for patients to use subcutaneous DFX for more than five days each week because of local problems at the infusion site, patients usually take deferiprone every day of the week. Compliance with DFX is substantially poorer than with deferiprone.^(15,16) Because of the differences in chelating properties between DFX and deferiprone, it has been essential to test the efficacy of deferiprone in long-term clinical trials. These have now been carried out in London,⁽¹⁷⁾ Toronto,⁽¹⁸⁾ Bombay⁽¹⁹⁾ and Switzerland.⁽²⁰⁾ In Toronto a randomised study comparing oral deferiprone with subcutaneous DFX is ongoing.⁽²¹⁾ The earliest studies in TM patients reported that serum

ferritin levels remained unchanged during 6–12 months of deferiprone therapy.^(11,18) Subsequently significant falls in serum ferritin have been found after 12 months or more of therapy, particularly among those patients with the highest initial iron burden.⁽²²⁾

For instance, in the Toronto trial patients with initial serum ferritin levels > 2500 mg/l showed a significant fall over a period of 12 months while those with initial serum ferritin levels < 2500 mg/l essentially showed no change.⁽¹⁸⁾ In Bombay, the previously most poorly chelated patients also showed the greatest fall in serum ferritin.⁽¹⁹⁾

Other tests of body iron burden have also showed an improvement in some patients. A significant fall in NTBI has been shown after six months of deferiprone therapy in eight patients.⁽²³⁾ Most importantly, liver iron has also been shown to fall in those patients with the highest initial concentrations.⁽¹⁸⁾ Among nine previously poorly chelated patients starting with liver iron concentrations > 80mmol/g liver net weight, seven showed levels below this level after 12 months or more of deferiprone therapy. All 12 patients with initial liver iron levels below 80mmol/l maintained these levels while receiving deferiprone therapy. A fall in liver enzymes in three of 10 patients treated for 11–12 months has also been reported.⁽²³⁾

As yet the evidence that cardiac or endocrine iron is reduced by deferiprone treatment in TM is scanty. This has been shown in a case of thalassaemia intermedia.⁽²⁴⁾ It seems likely that if there is a reduction of total body iron assessed by liver iron, serum ferritin, urine iron excretion and NTBI, a reduction of iron content in the organs generally will take place. In a case of thalassaemia intermedia, one year of deferiprone therapy did result in reduction of cardiac iron measured by magnetic resonance imaging (MRI).⁽²⁴⁾ Improvement in cardiac MRI findings among TM patients receiving deferiprone has also been suggested.⁽²⁵⁾ Anterior pituitary iron has also been shown to fall in two TM patients treated with deferiprone.⁽²⁵⁾ In our own recent studies, no overall change in cardiac function has been observed among 29 patients receiving deferiprone continuously for up to four years as assessed by MUGA scanning. Lightening of skin colour has been observed in both our own and the Indian studies.

Side Effects

Agranulocytosis

The first reported side-effects were agranulocytosis and thrombocytopenia in a woman aged 28 with Blackfan-Diamond anaemia who had received deferiprone (105 mg/kg/day for 6 weeks) and presented with severe septicaemia.⁽²⁶⁾ She had received a previous course of deferiprone, which had been discontinued after 10 weeks when she developed a rare LW red cell antibody, which subsequently disappeared. The thrombocytopenia, probably due to the severe infection, recovered after 10 days, the agranulocytosis after 3 weeks. No other instances of thrombocytopenia in patients receiving deferiprone have been reported, but further cases of agranulocytosis or severe neutropenia have occurred in at least 12 other patients with TM or myelodysplasia.⁽⁴⁾ The estimated incidence is 1–3% of all patients on long-term therapy. Nine of the 13 patients were female and all were severely iron overloaded. They presented between 6 weeks and 21 months after starting deferiprone therapy. All recovered, usually within 2–3 weeks but in one case 17 weeks after stopping the drug. Retreatment with deferiprone caused a

second fall in neutrophil count in all patients tested and should be avoided. In vitro studies have not shown any evidence of an immune or toxic mechanism.⁽²⁷⁾ No undue sensitivity of patients' recovery bone marrows (assessed by the CFU-GM assay) to the drug or its metabolites has been found. It seems most likely that an idiosyncratic sensitivity to the drug underlies the agranulocytosis; as with other drug agranulocytosis, females appear to be more susceptible than males.

Arthropathy

Muscle or joint pains, in some cases with joint effusions were first reported in four of 13 patients receiving deferiprone long-term.⁽²⁸⁾ Subsequently arthropathy has emerged as the most frequent side effect in some series. The knees and ankles are the joints most commonly affected. Usually the arthropathy settles on withdrawing deferiprone therapy or lowering the dose. In severe cases, with effusions, residual symptoms may be present several months after stopping deferiprone therapy. The Bombay study showed an increasing incidence of the arthropathy with increasing doses of the drug, three (10%) of 30 patients at a dose of 50 mg/kg/day, four (10%) of 40 at 75 mg/kg/day, but 20 (38.5%) of 52 at 100 mg/kg/day.^(19,29) Arthroscopy of affected joints has shown excess iron in synovium, cartilage and joint fluid but no deferiprone in the Indian studies. Berkovitch et al,⁽³⁰⁾ on the other hand, detected deferiprone in synovial fluid at a similar concentration to that in serum in three affected patients; no deferiprone-iron complexes were detected. The mechanism of the arthropathy, like that of the agranulocytosis, remains uncertain. No evidence for an immune aetiology has been established. The incidence of positive tests for anti-nuclear factor or rheumatoid factor is similar in TM patients before and after deferiprone therapy, and no correlation has been found between the presence of these antibodies and the development of arthropathy. A theoretical explanation for the arthropathy is that 1:1 or 2:1 complexes of deferiprone with iron instead of the normal 3:1 complexes may be formed in heavily iron-loaded joints, and it is these unstable complexes that leads to free radical damage. No experimental evidence exists for this or any other suggested explanation for the arthropathy.

Gastro-Intestinal Symptoms

These occur in a minority of patients and may be a cause for withdrawal of the drug. In our current studies, six of 56 patients developed nausea, anorexia or epigastric pains; in five patients, these were sufficiently severe to warrant permanent discontinuation of deferiprone therapy. Poor renal function with accumulation of deferiprone-glucuronide in plasma may have been responsible for nausea in one of the myelodysplastic patients, aged 80 years.⁽⁴⁾

Zinc Deficiency

Deferiprone is a relatively specific iron chelator with a high binding constant ($\log m=36$) and with a lower affinity for other metals. Zinc deficiency assessed by a subnormal serum zinc level was first reported in four of 10 patients after 7–13 months of deferiprone therapy.⁽¹⁰⁾ Urinary iron excretion increased above normal in eight of the 10 patients. The amount of zinc excretion could not be related to dose of deferiprone or iron

load of the patients. More recent studies have shown that zinc excretion is most increased in patients with diabetes mellitus, less so in patients with biochemical evidence of diabetes and least so in patients with normal glucose tolerance.⁽³¹⁾ In a few patients, clinical features of zinc deficiency—dry, itchy, scaling skin patches—have developed. The deficiency is easily corrected by oral zinc therapy, which does not impair iron chelation by deferiprone.

Liver Dysfunction

Rises in liver transaminase levels, often fluctuating have been reported in patients in several studies.⁽²²⁾ A substantial proportion of these patients have been anti-hepatitis C positive. No changes in serum bilirubin or alkaline phosphatase levels have been reported and no sustained rise in liver enzymes have occurred despite continuation of the drug.

Deaths

There are no published reports of patients who have died as a result of deferiprone therapy, but a number of patients have died while receiving deferiprone or soon after its discontinuation. These deaths have generally been in the older, more iron loaded, previously poorly chelated patients and usually from cardiac disease or, less frequently, infection. None of the infectious deaths have been associated with agranulocytosis. The suggestion that deferiprone causes immune deficiency⁽³²⁾ has not been substantiated by studies of B or T cell numbers, CD4, CD8 T lymphocyte counts, immunoglobulin levels and of lymphocyte function.^(4,5)

Conclusion

It is possible that deferiprone may become a licensed drug for the treatment of iron overload. The drug capable of maintaining or lowering body iron stores in transfusion-dependent patients. The side effect of agranulocytosis can be severe, but providing patients are carefully monitored and the drug discontinued if neutropenia develops, patients should recover. A 1–3% incidence of agranulocytosis may prove acceptable for a drug needed to save the lives of many thousands of transfusion-dependent patients worldwide, who cannot or will not take regular subcutaneous DFX. The other major side effect, arthropathy, is also reversible. Current long-term trials, providing they do not show unexpected new complications or a substantially higher incidence of agranulocytosis or arthropathy, should help to accelerate the licensing process.

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