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Deferiprone

A Review of its Clinical Potential in Iron Overload in β-Thalassaemia Major and Other Transfusion-Dependent Diseases

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Data Selection

Sources: Medical literature published in any language since 1966 on deferiprone, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand) and Medline. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'deferiprone' or '1-2-Dimethyl-3-hydroxypyrid-4-one' or 'CGP-37391' or 'CP-20' or 'L-1'. Medline search terms were 'deferiprone' or 'CGP 37391' or 'CP 020' or 'CP 20'. Searches were last updated 28 Jul 1999.

Selection: Studies in patients with iron overload who received deferiprone. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: deferiprone, thalassaemia, iron-overload, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Patients with β-thalassaemia and other transfusion-dependent diseases develop iron overload from chronic blood transfusions and require regular iron chelation to prevent potentially fatal iron-related complications. The only iron chelator currently widely available is deferoxamine, which is expensive and requires prolonged subcutaneous infusion 3 to 7 times per week or daily intramuscular injections. Moreover, some patients are unable to tolerate deferoxamine and compliance with the drug is poor in many patients.

Deferiprone is the most extensively studied oral iron chelator to date. Non-comparative clinical studies mostly in patients with β-thalassaemia have demonstrated that deferiprone 75 to 100 mg/kg/day can reduce iron burden in regularly transfused iron-overloaded patients. Serum ferritin levels are generally reduced in patients with very high pretreatment levels and are frequently maintained within an acceptable range in those who are already adequately chelated. Deferiprone is not effective in all patients (some of whom show increases in serum ferritin and/or liver iron content, particularly during long term therapy). This may reflect factors such as suboptimal dosage and/or severe degree of iron overload at baseline in some instances.

Although few long term comparative data are available, deferiprone at the recommended dosage of 75 mg/kg/day appears to be less effective than deferoxamine; however, compliance is superior with deferiprone, which may partly compensate for this. Deferiprone has additive, or possibly synergistic, effects on iron excretion when combined with deferoxamine.

The optimum dosage and long term efficacy of deferiprone, and its effects on survival and progression of iron-related organ damage, remain to be established.

The most important adverse effects in deferiprone-treated patients are arthropathy and neutropenia/agranulocytosis. Other adverse events include gastrointestinal disturbances, ALT elevation, development of antinuclear antibodies and zinc deficiency. With deferiprone, adverse effects occur mostly in heavily iron-loaded patients, whereas with deferoxamine adverse effects occur predominantly when body iron burden is lower.

Conclusion: Deferiprone is the most promising oral iron chelator under de-

velopment at present. Further studies are required to determine the best way to use this new drug. Although it appears to be less effective than deferoxamine at the recommended dosage and there are concerns regarding its tolerability, it may nevertheless offer a therapeutic alternative in the management of patients unable or unwilling to receive the latter drug. Deferiprone also shows promise as an adjunct to deferoxamine therapy in patients with insufficient response and may prove useful as a maintenance treatment to interpose between treatments.

Pharmacodynamic Properties

Deferiprone is an oral bidentate iron chelator which binds to iron in a 3 : 1 ratio. It also binds other metals including aluminium, gallium, copper and zinc, but not calcium or magnesium.

Deferiprone reduces body iron content in iron-overloaded animals and humans. Iron excretion is related to dosage and the degree of iron overload, and occurs largely by the renal route. Deferiprone appears to mobilise iron from both reticuloendothelial and hepatocellular pools, from transferrin, ferritin and haemosiderin and from pathological iron deposits in intact red blood cells from patients with thalassaemia or sickle-cell anaemia.

Depending on concentration, deferiprone has been reported to promote (at low concentrations, *in vitro*), and conversely to protect against (at high concentrations), oxidative damage caused by oxygen free radicals.

As with deferoxamine, deferiprone inhibits proliferation of several cell lines *in vitro* and may induce apoptosis. It has also shown myelosuppressive effects in animals and humans. Although *in vitro* data suggest that deferiprone is markedly less toxic than deferoxamine to bone marrow myeloid progenitors, the clinical relevance of this is unclear, as deferiprone-induced myelosuppression may occur via a reactive metabolite-induced event mediated by the immune system.

Pharmacokinetic Properties

Peak plasma concentrations (C_{max}) are reached within approximately 1 hour after oral administration of deferiprone. Food intake reduces the rate, but not the extent, of absorption of the drug. Administration of deferiprone 75 mg/kg/day at 12-hourly intervals produced a C_{max} of 34.6 mg/L and area under the plasma concentration-time curve (AUC) of 137.5 mg/L · h in patients with β-thalassaemia. Coadministration of iron (ferrous sulfate 600mg) reduced the AUC by about 20% in healthy volunteers.

It is not clear whether deferiprone induces its own metabolism *in vivo*. This has been demonstrated *in vitro*. Trough plasma concentrations of deferiprone decreased during long term treatment with the drug in 1 study, but this was not corroborated by other studies.

The volume of distribution after administration of deferiprone 75 mg/kg/day was 1.55 or 1.73 L/kg at steady state (depending on the dosage schedule) in patients with β-thalassaemia. Deferiprone was found to accumulate (≈3-fold) in thalassaemic, but not normal or sickle, red blood cells *in vitro*.

Deferiprone is metabolised predominantly (>85%) to a glucuronide conjugate that lacks chelating properties. The drug, its conjugate and the deferiprone-iron complex are mainly excreted by the kidney and approximately 80% of a dose is recovered in the urine. Deferiprone is rapidly eliminated, with an elimination half-life ($t_{½\beta}$) of approximately 1 to 2.5 hours in patients with β-thalassaemia. The $t_{½\beta}$ of deferiprone glucuronide was significantly correlated with creatinine clearance and this metabolite was found to accumulate in a patient with renal dysfunction. Although deferiprone is metabolised by the liver, the effects of hepatic impairment on the pharmacokinetics of the drug are yet to be determined.

Therapeutic Potential

Clinical studies, mostly in patients with β-thalassaemia, have demonstrated that deferiprone 75 to 100 mg/kg/day is capable of reducing iron burden in regularly transfused iron-overloaded patients. Factors affecting response to deferiprone appear to include the degree of iron overload and duration, dosage and degree of compliance with therapy.

Serum ferritin levels (an indirect indicator of body iron load) are generally decreased in patients with very high pretreatment levels. In patients who are already adequately chelated at baseline, serum ferritin levels frequently remain stable. However, increases or inadequate decreases in serum ferritin and/or hepatic iron content were seen in some patients, especially after long term treatment. In some instances, this may reflect suboptimal dosage and/or severe degree of iron overload at baseline. Beneficial effects noted in some long term studies include lightening of the skin and decreased serum ALT and non-transferrin-bound iron levels.

It should be noted that long term clinical trials reported to date have generally been noncomparative and conducted in small numbers of patients, who differed greatly with regard to baseline chelation status and underlying disease. Moreover, in many studies, the proportion of patients who were adequately chelated on deferiprone was not reported.

Short term comparative studies have demonstrated that deferiprone ≤75 mg/kg/day is less effective than deferoxamine in increasing iron excretion. However, compliance during clinical use is superior with deferiprone, which may compensate for this to some degree. Few data from long term prospective randomised studies comparing deferiprone with deferoxamine have been reported. In these studies, deferiprone appeared to be slightly less effective than deferoxamine in reducing serum ferritin and less effective in controlling hepatic iron levels.

Preliminary data suggest that deferiprone can be used successfully in combination with deferoxamine, with additive or synergistic effects on urinary iron excretion and substantial reductions in serum ferritin levels being achieved.

Tolerability

The most common adverse events in deferiprone-treated patients have been arthropathy (musculoskeletal stiffness and pain, accompanied by effusion in severe cases) and gastrointestinal disturbances (anorexia, nausea, vomiting). Arthropathy occurred in up to 39% of patients in clinical trials and generally resolves on dosage reduction or drug withdrawal.

The most serious adverse effect associated with deferiprone is severe neutropenia/agranulocytosis (approximately 2% of patients each). This appears to be reversible.

Other adverse events include elevated ALT and immunological abnormalities (development of antinuclear and antihistone antibodies). Deferiprone also promotes increased urinary excretion of zinc, particularly in patients with diabetes mellitus. This may occasionally lead to clinical signs of zinc deficiency (e.g. dry/itchy skin), which respond to zinc supplementation.

Progression of existing liver fibrosis in 5 of a series of 14 patients treated with deferiprone was attributed to the drug, but this conclusion was subsequently questioned on the basis of methodological flaws in the study concerned. Long term follow-up of deferiprone-treated patients by other investigators implicates chronic hepatitis C infection and iron overload, rather than deferiprone, in progression of hepatic fibrosis in transfusional iron-overloaded patients.

Dosage and Administration

The recommended dosage of deferiprone is 25 mg/kg 3 times daily, although some investigators recommend use of dosages up to 100 mg/kg/day and/or twice daily administration. Special monitoring is required in all patients. Particular caution is recommended (with monitoring of renal or hepatic function) when treating patients with impaired renal or hepatic function. Deferiprone is contraindicated in patients with neutropenia or a history of agranulocytosis or recurrent episodes of neutropenia, those taking drugs known to cause neutropenia, and in pregnant or lactating women. Women of childbearing potential should use contraceptives while taking deferiprone. Weekly monitoring of neutrophil count is recommended and patients should be advised to report immediately any symptoms of infection, such as fever, sore throat or flu-like symptoms.

Deferiprone may interact with concomitantly administered medications containing metallic cations, including aluminium-based antacids.

1. Introduction

Thalassaemia major is one of the most common worldwide causes of iron overload. The thalassaemias are a heterogeneous group of hereditary haemolytic anaemias characterised by inadequate synthesis of one or more haemoglobin polypeptide chains. They are classified according to which chain is involved (α, β or δ). In β-thalassaemia, decreased β-chain production leads to a relative excess of α-chains, which are unstable.

Patients with β-thalassaemia major (or Cooley's anaemia; the most severe form of the disease) usually manifest symptoms at 4 to 6 months of age, developing severe anaemia with a haematocrit of <20%. They require regular blood transfusions in order to avoid the complications of anaemia and ineffective erythropoiesis, allow normal growth and development and prevent early death. However, iron from the transfused blood accumulates in the reticuloendothelial system and parenchymal cells.

Iron toxicity begins when the load of iron in a particular tissue exceeds the binding capacity of ferritin in the cell and of transferrin in the plasma. This results in accumulation of free or non-transferrin-bound iron (NTBI), which can participate in free radical formation, leading to peroxidation and damage in various tissues. As reviewed by Olivieri and Brittenham[1] the degree of clinical iron toxicity in iron-overloaded patients is determined by:

- the amount of excess iron
- the rate of iron accumulation
- the duration of exposure to elevated iron levels
- the distribution of iron between highly hazardous and less hazardous body sites
- ascorbate status (which influences body distribution of iron)
- presence of viral hepatitis
- alcohol intake.

The sequelae of iron overload include hepatic fibrosis and cirrhosis, multiple endocrinopathies (diabetes mellitus, hypogonadism, hypoparathyroidism, hypothyroidism), immunological dysfunction, growth and bone abnormalities, short stature, cardiac disease (congestive heart failure, arrhythmias), pulmonary dysfunction and hyperpigmentation of the skin. Progressive organ dysfunction, affecting the heart, liver and endocrine system in particular, ultimately leads to death in the second or third decade of life if left untreated.

A high proportion of regularly transfused thalassaemic patients have hepatitis C acquired via transfused blood, whereas vaccination has drastically decreased the incidence of hepatitis B in this population.

The management of thalassaemia and iron overload has been reviewed by other authors.[1-6]

The iron-chelating agent deferoxamine has been available for over 2 decades. Effective chelation with this agent maintains body iron stores in patients with thalassaemia major at 5 to 10 times the levels found in healthy individuals.[7] Nevertheless, with this level of control of body iron, patients

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