Editorial

ORAL IRON CHELATORS

Many disorders in hematology, especially thalassemia major and allied conditoins, result in severe iron overload secondary to repeated transfusions. Desferrioxamine, although cumbersome to use and expensive, has been the only effective iron chelator so far. The need for an oral drug making chelation simpler was felt for the last 3 decades and over 500 compounds have been investigated in experimental studies. All these attempts were largely unsuccessful as either the compounds were ineffective or too toxic for lifelong therapy. There is no doubt that desferriox-amine has successfully prolonged lifespan of thousands of patients all over the world. In addition, its safety profile has been very satisfactory(1).

The untiring efforts of Kontoghiorghes and his group over the last 15 years have finally resulted in marketing of the only other iron chelator *viz.* deferiprone or 1,2-dimethyl-3-hydroxypyrid-4-one (L1)(2-7). After initial laboratory studies, many *in vitro* and *in vivo* studies and clinical trials were carried out to identify the metabolic, pharmacological and toxicological properties of L1. Prior to this, more than a dozen iron chelators which were effective by oral route, failed to withstand the test of time. For the first time, an oral iron chelator, L1 was continuously studied in over 800 patients of different disorders (chiefly thalassemia) at centres in London, Toronto, Bombay, Berne, Italy (Milan, Cagliari, Massina) and Amsterdam *etc.* These patients were in the age group of 2-85 years and were given L1 for variable periods extending upto 5 years. Overall 10 different categories of patients have received L1, of which thalassemia alone accounts for about 80%(6).

The Bombay study at L.T.M. Medical College, Sion and J.J. Group of Hospitals) took off in 1989 and was soon extended to AIIMS (Delhi), PGI (Chandigarh) and Kothari Institute of Medical Sciences (Calcutta)(8) to include over 200 patients(9,10). The product was finally approved by the Drug Controller of India in February 1995 for use in patients of iron loaded transfusion-dependent thalassemia. The available preclinical as well as clinical data on L1 is summarized below.

L1 appears to be slightly less effective than desferrioxamine in bringing patients to negative iron balance, in increasing urinary iron excretion, reducing liver iron and serum ferritin levels(11-15). As desferrioxamine removes l/3rd of iron in stool as well, the effective daily dose of L1 is 75-100 mg/kg/day (the same for desferrioxamine being 30-60 mg/kg/day). Many patients have received L1 in these doses for years with drop in serum ferritin level to near normal range(6,9,10,13,14). The daily urinary iron excretion at a given dose is variable but results in a negative iron balance(7). Besides iron load of the

patient, many other ill-defined factors play a role in this variability. Frequency of administration, relationship to meals and addition of ascorbic acid do not have a significant role in increasing urinary iron excretion(7,10).

L1 is metabolized by glucuronidation and the L1-glucuronide conjugate has no chelation properties. L1, L1 iron complex and L1-glucuronide conjugate are all excreted in the urine. The factor affecting glucuronidation remain largely unknown(6). There is also a suggestion that iron chelation precedes glucuronidation and if that is true, this pathway of metabolism may not affect the clinical efficacy of the drug(6).

The iron metabolized by L1 comes from at least 3 different sources (i) low molecular weight serum iron in excess of transferrin saturation; *(ii)* transferrin bound iron; *(iii)* intracellular iron from liver and other organs.

The main obstacle to L1 rapidly becoming a widely available drug has been the occurrence of adverse effects. L1 has a narrow therapeutic index. The mechanisms by which side effects occur are ill-understood(7,9,16,17). The most serious side effect is myelotoxicity which although dose-related, has occurred in 1-2% of patients in an unpredictable fasion(7,10). Acute agranulo-cytosis and chronic neutropenia are reported. Regular monitoring of blood counts is, hence, essential throughout L1 therapy. Both agranulocytosis and neutropenia appear reversible. Administration of granulocyte colony stimulating factor may shorten the period of neutropenia by stimulating neutrophil production. Occurrence of this complication should contraindicate further use of this drug(7,10). Interestingly, no such cases have been reported from the Canadian(12,13,18) and Swiss(14) trials, but that could be due to small number of cases and lower doses of L1. The risk of myelotoxicity is an important reason why L1 has not been used in patients with pre-existing marrow disorders like myelodysplasia and Diamond-Blackfan syndrome.

Arthralgia, arthritis and vague muscle pains occur in about 10-30% of patients(7,9-ll,19). The most commonly affected joint is the knee and although the mechanism remains uncertain, there is no evidence that it is related to rheumatoid arthritis or systemic lupus erythema tosus like syndromes(20,21). Many of these patients improve and become asymptomatic on reducing the dose of Ll(7,9-11). Studies have shown iron deposition in the cartilage, synovial membrane and the synovial fluid. These side effects appear related to the initial iron overload, higher dose of L1 and abnormal liver function(10). Various suggestions regarding the cause of L1-arthropathy syndrome include: accumulation of toxic form of iron in the joints and inhibition of a metallo-enzyme involved in the detoxification of toxic free oxygen radicals. Occasional patients have developed significant articular cartilage damage especially if treatment with L1 is continued and hence care must be taken(10).

Zinc deficiency of a mild nature has occurred in occasional patients with thalassemia, chiefly in those with secondary diabetes. Despite enhanced urinary zinc excretion, majority of patients maintain normal serum zinc levels and

hence no prophylactic supplement or special diets are required(10). Patients showing dermatopathy secondary to zinc deficiency (itchy, scaly rash and hair loss) should be given zinc supplements. Treatment with LI need not be discontinued in these cases(7).

Being an oral drug, 2-5% of patients show anorexia, nausea, vomiting and abdominal discomfort(7,9-11). There is no evidence of hepato or nephrotoxicity. Even with high doses, no patients have shown ear or eye toxicity or -an adverse effect on growth(7,9-11).

It appears that in 70-80% of patients L1 is a satisfactory, orally active iron chelator and may be used alone lifelong. About 10-20% patients tolerate a lower dose of L1 and treatment may have to be combined with desferrioxamine. In a minority (5-10%), L1 therapy has to be withdrawn because of side effects.

L1 is teratogenic in animal studies and hence should not be given to a woman who is pregnant or likely to become pregnant(22).

Although usually considered as an anemia common in the Mediterranean region, 80-90% of thalassemics live in the developing world(23). Desferrioxa-mine has never been used in lifesaving doses by 95% of thalassemics in this part of the world(23). Compliance with desferrioxamine is a common and serious problem even in the developed world. Unfortunately, none of the other iron chelators including HBED and 90 other alfa-ketohydroxypyridines tested in animals, appear promising enough to be of clinical use(24-27). Earlier studies using CP 94 appeared promising but the drug was abandoned following disappointing clinical results. Some of the newer compounds like 1-ethyl-2-methyl-3-hydroxyprid-4-one (LINEt) appear attractive. Long term studies would be required to document its efficacy over L1.

On the basis of available information L1 is an effective iron chelator. Presence of significant side effects requires that the drug be used under careful medial supervision. However, in view of the life threatening complications faced by most thalassemics secondary to iron overload, use of this drug is imperative. The introduction of L1 in the market is an important advance in the management of children with thalassemia.

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