Indian J Pediatr 1993; 60 : 509-516

Oral Iron Chelation : A Review with Special Emphasis on Indian Work on Deferiprone (L_1)

M.B. Agarwal

Division of Hematology, Department of Medicine, L.T.M.G. Hospital and L.T.M. Medical College, Sion, Bombay

Due to the high cost and inconvenient mode of administration of desferrioxoxamine (DFO), search has been on to find an orally effective, non-toxic and cheaper iron chelator for quite some time.[1] During the last thirteen years, deferiprone or 1,2- Dimethyl-3-Hydroxypyridin-4-One under various names i.e. CP_{20}; DMHP, CGP 37 391, or L_1 has by far received the most attention.[2-9] It has undergone extensive preclinical and clinical studies for fairly long period, and barring a few isolated incidences of adverse reactions chiefly related to marrow toxicity and arthropathy, it appears to fulfil majority of requirement so as to replace DFO therapy.[2-13] It is estimated that since the beginning of the clinical trial in 1987, over 400 patients aged between 2-82 years from 26 centres belonging to 14 countries have taken deferiprone for variable periods upto 48 months maximum.[14] Although iron overloaded thalasemics form the commonest of the condition, it has been used for over 10 disorders where iron overloading occurs.[15] There has been substantial Indian contribution in assessing the exact position of deferiprone in iron loaded thalassemics during the last 4 years, and there has been serious talk about making the compound available for more extensive work both in developing and developed countries.[5-7,16] Hence it would be timely to review the exhaustive preclinical and clinical data available on this compound as of today. Following is an attempt in the same direction.

Two hundred and forty million of the world's population are heterozygous for thalassemia or abnormal haemoglobin.[17] About 1 lakh children are born each year worldwide with transfusion-dependent thalassemia.[17] Out of this, at least 5,000 children are born in India alone.[17] Many of them die without diagnosis or even after diagnosis due to lack of blood. However, number of children receiving regular transfusions is gradually increasing and hence demand for iron chelation is increasing.[17] Treatment with subcutaneous DFO is effective only if it is given over 8 hours per day, 5 days a week starting from the first 2 or 3 years of life. This is why only a few patients of thalassemia have crossed the 3rd decade of life and deaths secondary to iron induced cardiac as well as liver disease occur.[17] In India, 98% of patients with thalassemia do not receive any DFO treatment and thus die by 15-20 years of life.[17] On the other side, a small country like Cyprus has to spend approximately 50% of their drug budget on DFO alone.

It is against this background that, worldwide, over 500 chelators have been

Reprint requests : Dr. M.B. Agarwal, Haematology Centre, Vijay Sadan, 168, B. Ambedkar Road, Dadar T.T., Bombay-400 014.

tested in laboratories as well as animal experiments so as to obtain a chelator which is orally effective, cheap and non-toxic.[18] Only less than a dozen of them have reached the stage of clinical trials, but most of them had to be abandoned due to major toxic side effects or ineffectiveness.[18]

Major breakthrough in this field has been achieved in the last 5 years, and that is essentially due to the development of compounds belonging to the group-Hydroxypyridones specially 1,2-Dimethyl-3-Hydroxypyridin-4-One.[1] This drug has recently adopted the British approved name and International Non-proprietary name Deferiprone.[15] In number of studies carried out worldwide, deferiprone has been shown to be effective both in animals and men in short term as well as fairly long term clinical trials extending upto 3-4 years.[4,7] Clinical trials are ongoing at U.K.[2] Canada,[19] India,[16] Switzerland[4] and other places.[15] The results available so far are extremely encouraging.[14]

Pharmacology of Deferiprone

For a chelator to be effective orally, it has to be suitable in acidic atmosphere of the stomach, and to establish the therapeutic protocol one needs to know its site and rate of absorption as well as the rate of biotransformation. One also needs to know the effect of other dietary constituents on the absorption of the drug, specificity of the chelator with respect to iron chelation, its effect on the absorption of iron and other trace metals from the gut, extent of its reabsorption, details of its metabolism and resultant metabolites, excretion pattern of the drug and its metabolite, degree of variations in the rate of absorption, metabolism and excretion of the drug and its metabolites, etc.[14,20-25]

Kontoghiorghes and his group have shown that deferiprone is stable at physiological and acidic pH.[14] It is absorbed from stomach. Its main metabolite is a glucuronide conjugate which is formed in liver and cleared through the kidney with a half of 45-120 minutes. Urine contains all the 3 compounds, i.e. unchanged drug, drug-iron complex as well as glucuronide conjugate. Iron excretion is essentially in urine and hardly any drug or drug-iron complex is detectable in faeces. Iron absorption from the gut is not enhanced by deferiprone.[14]

The iron excreted by deferiprone in urine increases with the increasing dose of deferiprone (Table 1).[6] It is also related to the iron load of the patient (Table 2)[7] as well as frequency of administration of the drug.[14] The iron mobilised by deferiprone in iron loaded thalassemics is chiefly from serum transferrin and liver cells but possible from other cells and tissues as well. This is highly significant as serum transferrin is in equilibrium with all the iron pools such as beam or iron ferritin and hemosiderine.[14] Thus, deferiprone treatment would lead to gradual de-ironing of most of the tissues. This, however, is a slow process

TABLE 1. Data on Urinary Iron Excretion on Different Doses of Deferiprone (n=52)

Dose of Deferiprone (mg/kg/d)	Urinary iron (mg/24 h)	
	Mean	Range
Nil	1.2 ± 0.3	0.2 - 2.5
25	6.2 ± 4.6	1.1 - 16.4
50	15.7 ± 9.1	2.4 - 26.9
75	26.9 ± 20.7	11.2 - 74.9
100	42,3 ± 17.1	18.4 - 110.4

TABLE 2. Correlation Coefficients of Urinary Iron Excretion at Different Dose Levels of Deferiprone Therapy with Age, Weight, Serum Ferritin and Amount of Blood Transfused.[7]

Deferiprone dose (mg/kg/d)	Correlation coefficients (P value) with :			Quantity of blood transfused
	Age	Weight	S.ferritin	
25	0.0116 (n.s)	0.0273 (n.s.)	0.2232 (n.s.)	0.0637 (n.s.)
50	0.3439 (p<0.05)	0.0623 (n.s.)	0.4470 (p<0.001)	0.1785 (n.s.)
75	0.2829 (p <0.05)	0.2843 (p<0.05)	0.2804 (p<0.05)	0.1785 (n.s.)
100	0.3932 (p <0.005)	0.2416 (p=0.05-0.1)	0.3227 (p <0.05)	0.0426 (n.s.)

n.s. : not significant.

and takes years to complete. The process can be enhanced by frequent administration of the drug, i.e. every 3-4 hourly.[14]

Clinical Efficacy

Clinical trials have shown marked lightening of the skin colour as well as disappearance of the black line over the gums within 3-6 months of deferiprone therapy which is a great moral booster to the patients.[7] Number of studies have shown that the daily iron excretion at a dose of 75 mg/kg/day or more of deferiprone is adequate (i.e. over 0.5 mg/kg/day) to achieve negative iron balance in 82.5% of patients[7] (Table 3). It has also been shown that a dose of 50 mg/kg/day is inadequate for this purpose in 73.3% of patients[16] (Table 3). Serum ferritin starts dropping within 3-6 months of deferiprone therapy. By the end of 14-20 months it invariably drops significantly (i.e. by 50%) in all the patients (Table 4).[7] Many patients achieved S.ferritin levels of below 2000 ng/ml in 12-18 months despite continuous transfusions.[16] Those with initial level of serum ferritin below 2000 ng/ml are able to maintain this level.[16] However, aggressive iron chelation with higher dose can bring it down even further. Transfusion independent but still iron loaded thalassemia intermedia patients (where iron overload is due to G.I. tract iron absorption) show a rapid decline in serum ferritin as well as liver iron content.[16]

Urinary iron excretion following

TABLE 3. Efficacy of Deferiprone : Urinary Iron Excretion

Deferiprone dose (no. of pts)	50 mg (30)	75 mg (40)
Urinary iron		
(a) Absolute mg/d	18.9 ± 12.3 (3.3 - 32.3)	30.5 ± 24.2 (14.6 - 71.5)
(b) > 0.5 mg/kg/d	8/30 (26.7%)	33/40 (82.5%)

TABLE 4. Drop in *S.ferritin* on Deferiprone Therapy[7]

Duration of treatment (months ± SD)	No. of patients	Absolute drop ± SD (ng/ml)
20.1 ± 0.9	11 (21.2%)	3641.2 ± 2299.3 (>50%)
14.9 ± 1.2	14 (26.9%)	2373.1 ± 1927.3 (>50%)
9.2 ± 2.2	19 (36.5%)*	1798.6 ± 1205.0
5.0 ± 0.8	8 (15.4%)@	1465.0 ± 990.0

* One case, : no drop; one case, : rise.
@ Two cases, not analysable; two cases, rise.
(*,@ Excluded from this analysis)

TABLE 5. Efficacy of Deferiprone versus DFO (five patients)[7]

Case	Urinary iron excretion (mg/24 h)	
	Deferiprone 50 mg/kg/d (b.d.)	DFO 50 mg/kg/d (b.d.) (over 12 h) (s.c.)
1	18.2	19.6
2	15.6	26.5
3	12.5	11.3
4	11.3	9.6
5	29.3	40.3
Mean	17.4 ± 7.2	21.5 ± 12.5 p:n.s

n.s. : not significant

deferiprone and DFO (on equivalent doses) is almost similar[7] (Table 5). Hence the efficacy of deferiprone can be made to be 2/3rd as that of DFO. This is because DFO excretes 1/3rd of iron in faeces as well. However, deferiprone can be easily administered daily without interruption while most of the protocols related to DFO omit the treatment at weekends so as to increase the compliance.[7]

Adverse Effects

Long term use (upto 4 years) of deferiprone in clinical trials have now established that the adverse effects following its administration are essentially in the form of isolated incidence of transient toxicity[2-4,7] (Table 6). Most of the over 400 patients put on deferiprone have been able to continue the drug without any complaints or apparent complications.[15]

DFO has been around for over quarter of a century and therefore its adverse effects are reasonably well-known. Still one must accept that the story may not have unfolded itself fully and every new year some or the other new adverse reaction is identified and published. Besides local problems at the site of injections, it is

TABLE 6. Adverse Effects : (100 mg of Deferiprone/kg/d)[7] (n=52)

Symptoms	No. of patients
Mild GI symptoms	7 (13.5%)
Altered LFT	2 (3.8%)*
Joint pain	16 (30.8%)@
Swelling of knee joints	4 (7.7%)

* Both patients had post-transfusion viral hepatitis
@ Knee (all), lower back (4), hips (2), elbows (2), myalgia (2), fever (1).

known to produce occasional anaphylactic reactions. If given in high doses to less severely iron loaded patients, it produces ocular, auditory and neurotoxicity.[14] In addition, there are problems of growth failure, bony abnormalities, yersiniasis, mucormycosis and also pulmonary toxicity. Fortunately, none of the clinical studies using deferiprone have yet shown any of these side effects.[14]

Table 7 enlists updated adverse effects secondary to deferiprone as seen by us during last 4 years. These are different from those seen with DFO. Also, most of these adverse effects appear to be dose related (Table 6 & 7). Any oral compound is bound to produce a mild gastrointestinal intolerance in a small number of patients and so is with deferiprone (5%).[7,16] The most significant complications have been : (i) myelotoxicity i.e. occurrence of neutropenia in 4 cases,[2,11,16] (ii) arthropathy i.e. skeletomuscular pain and/or swelling specially around the knee and hip joints in 10-30% of cases,[5,7] (iii) mild zinc deficiency occasionally leading to dermatopathy (1%),[2,16] (iv) questionable occurrence of immunological complications, e.g. lupus-like syndrome.[10] This however is not documented in most of authentic long term studies carried out at different centres.[14]

Both myelotoxicity and arthropathy secondary to deferiprone are reversible.[7] The exact mechanism of marrow toxicity by deferiprone is unknown.[7] However, it appears to be an idiosynchretic reaction and may be secondary to formation of reactive metabolites as previously described for other drugs.[14] The arthropathy is due to redistribution of iron into synovial membrane as well as articular cartilage.[16] It is related to high initial iron overload of the patients (Table 8) and a higher dose of deferiprone.[16] Viral or iron induced liver dysfunction may also produce certain alterations in drug metabolism leading to

TABLE 7. Deferiprone : Adverse Effects Over 4 years

Adverse effects	Dose (50 mg) (n=30)	Dose (75 mg) (n=40)	Total (n=70)
	No. of patient's & percentage		
Arthropathy	3 (10%)	4 (10%)	7 (10%)
G.I. symptoms	2 (6.7%)	3 (7.5%)	5 (7.1%)
Insomnia and drowsiness	1 (3.3%)	2 (5%)	3 (4.3%)
Neutropenia	-	1 (2.5%)	1 (1.4%)
Zinc deficient dermatography	-	1 (2.5%)	1 (1.4%)
Priapism	-	1 (2.5%)	1 (1.4%)
	6 (20%)	12 (30%)	18 (25.7%)

TABLE 8. Arthropathy : Effect of Initial Iron Overload

	Arthropathy (n=7)	No arthropathy (n=63)
Initial S.ferritin (ng/ml)	4720 ± 2668	2392 ± 1863

$p < 0.05$

these complications.[16]

Urinary zinc excretion increases with deferiprone. But, serum zinc levels have only occasionally been shown to drop below normal level and the skin patches or alopecia have been rare events[16] (1% of patients). More serious complications due to zinc deficiency have not been described and the mild changes mentioned above reverse on zinc supplementation,[16] which has so far been needed in only 2 patients (out of over 400 patients).[2,16]

Occurrence of lupus-like syndrome in a single patient on deferiprone appears controversial.[7,26,27] Variable alterations in certain immunological tests like antinuclear factor (ANF) and rheumatoid factor (RF) following deferiprone therapy have been described.[7,27] However, most of them remain laboratory observations.[16] They have no correlation with arthropathy (Table 10).[7] Also, chronic liver disease secondary to viruses produces significant alterations in these parameters.[20] Most of the long term clinical studies (form Switzerland, India, U.K. and Canada) have looked at this problem carefully and the results have failed to correlate deferiprone with immunological alterations.[7,16] Many patients without chelation or on DFO show similar incidence of ANF or RF positivity and hence as of today, immunological parameters appear to lack specificity with reference to skeletomuscular complications.[28]

TABLE 9. Arthropathy : Incidence and Effect of Dose

Dose/kg	100 mg	75 mg	50 mg
Duration (mo)	14.2 ± 6.8	18	18
Number of patients	20/52 (38.5%)	4/40 (10%)	3/30 (10%)

Other Oral Iron Chelators

Three other compounds belonging to hydroxypyridone group namely, L_1NEt, L_1NCPr and L_1Nall as well as N-N'-bis (O-hydroxybenzyl) ethylene-diamine-N-N' - diacetic and acid (HBED) are in the process of being tested in men. One has to show their advantage over deferiprone either in efficacy or with reference to adverse effects.[14] The advantage of deferiprone at the moment is availability of significant clinical data (extending upto 4 years) with respect to its efficacy and adverse effects, its low cost of production and wide acceptability around the world.[14,29-30] Compounds like HBED, although effective, are very expensive (like DFO) and data regarding adverse effects in humanbeings still have to be worked out. Recent clinical work has raised doubt about its efficacy.[14]

CONCLUSION

Deferiprone appears to be strongly knocking the doors of iron chelation therapy. It is a cheap, easy to manufacture, effective and reasonably safe oral iron chelator. Only occasional patients cannot benefit from its use as they suffer from skeletomuscular pain or myelotoxicity. These toxic effects are largely reversible. Such unfortunate

TABLE 10. Deferiprone-Related Arthralgia : Immunological Studies[7]

Test	TM with Deferiprone-related arthralgia (20) Initial	Final	TM on Deferiprone (no arthralgia) (32) Initial	Final	TM (83) (control group not on Deferiprone)	Normal (no TM) (52)
ANF (≥ 1 : 80)	2(10%)[a]	5(25%)[b]	4(12.5%)[c]	5(15.6%)[d]	12(14.5%)[e]	1(1.9%)[f]
RF (≥ 1 : 80)	2(10%)[a]	3(15%)[b]	2(6.3%)[c]	3(9.4%)[d]	5(6%)[e]	(Nil)[f]

ANF : P value : a v b, ns; c v d, ns; b v e, ns; d v e, ns;
RF : P value : a v b, ns; c v d, ns; b v e, ns; d v e, ns.
TM : Thalassemia major. ns : not significant.

individuals have to resort back to expensive and inconvenient DFO therapy. There appears to be very little justice in depriving the remaining population from the advantages of deferiprone. Without iron chelation, death of a thalassemic by 15-20 years is certain. Delay in starting of iron chelation may not prevent such deaths. From this angle alone, deferiprone should be introduced as an alternative treatment to DFO whenever the patient has a choice between no chelation versus deferiprone. It has the ability to improve the quality of life of patients receiving lifelong transfusions.

ACKNOWLEDGEMENTS

I acknowledge the guidance obtained from Professor A.V. Hoffbrand, Dr. George J. Kontoghiorghes and Dr. B. Wonke, Royal Free Hospital School of Medicine, London, and thank them for their continued advice and help during the trial. I also thank CIPLA Ltd., India for financially supporting this trial.

REFERENCES

1. Kontoghiorghes GJ. New orally active iron chelators. *Lancet* 1985; 1 : 817.
2. Bartlett AN, Hoffbrand AV, Kontoghiorghes GJ. Long-term trial with the oral iron chelator 1,2-dimethyl 3-hydroxypyrid-4-one (L1). II Clinical Observations. *Br J Haematology* 1990; 76 : 301-304.
3. Olivieri NF, G, Koran C, St Louis P et al. Studies of the oral chelator 1,2-dimethyl-3-hydroxypyrid-4-one in thalassemia patients. *Semin Hematol* 1990; 27 : 101-104.
4. Toendury P, Kontoghiorghes GJ, Ridolfi-Luthy A et al. L_1 (1,2-dimethyl-3-hydroxypyrid-4-one) for iron chelation in patients with beta-oral major. *Br J Haematol* 1990; 76 : 550-553.
5. Agarwal MB, Viswanathan C, Ramananthan J et al. Oral iron chelation with L1 (letter). *Lancet* 1990; 335 : 601.
6. Agarwal MB, Gupta SS, Vasandani D. Efficacy and safely of 1,2-dimethyl-3-hydroxypyrid-4-one (L1) as an oral iron chelator in patients of beta thalassemia major with iron overload. *Journal Assoc Phys of India* 1991; 39 : 669-672.
7. Agarwal MB, Gupta SS, Vishwanathan C et al. Long term assessment of efficacy and safely of L1. an oral iron chelator, in transfusion dependent thalassemia India trial. *Br J Haematol* 1992; 82 : 460-466.
8. Kontoghiorghes GJ. L1. 1,2-dimethyl-3-hydroxypyrid-4-one. *Drugs of the Future* 1988; 13 : 413-415.
9. Kontoghiorghes GJ, Aldouri MA, Hoffbrand AV et al. Effective chelation of iron in beta thalassemia with the oral chelator 1, 2-dimethyl-3-hydroxyphrid-4-one. *Br Med*

J 1987; 295 : 1509-1512.
10. Mehta J, Singhal S, Revankar R et al. Fatal systemic lupus erythematosus in patient taking oral iron chelator L1 (letter). *Lancet* 1991; 337 : 298.
11. Hoffbrand AV, Bartlett AN, Veys PA et al. Agranulocytosis and thrombocytopenia in a patient with Blackfan-Diamond anaemia during oral chelator trial (letter). *Lancet* 1989; 2 : 457.
12. Kontoghiorghes GJ et al. Safety of oral iron chelator L1. *Lancet* 1989; 2 : 457.
13. Kontoghiorghes GJ, Nasseri-Sina P, Goddard JG et al. Safety of oral iron chelator L1 (letter). *Lancet* 1989; 2 : 4578.
14. Kontoghiorghes GJ. Advances in oral iron chelation in man : A review. *Int J Hematol* 1992; 55 : 27-38.
15. Kontoghiorghes GJ. Updated report on the worldwide oral iron chelation therapy with L1-deferiprone and ketohydroxypyridone (abstract). *5th Int Conf on Thalassemia and Haemoglobinopthies* held at Cyprus, 1993; pp. 111.
16. Agarwal MB, Gupta SS, Vishwanathan C et al. Long term efficacy and toxicity of L1 - oral iron chelation in transfusion dependent thalassemics over the last three years (1989-92) (abstract) : *5th Int Conf on Thalassemia and Haemoglobinopathies* held at Cyprus. 1993; pp. 192.
17. Agarwal MB. *Living with Thalassemia.* Bombay : Bhalani Book Dept, 1986.
18. Grady RW, Graziano JH, White GP et al. The development of new iron chelating drugs (ii). *Journal of Pharmacology and Experimental Therapeutics.* 1978; 205 : 757-765.
19. Olivieri NF, Koren G, Klein J et al. Oral iron chelation with 1,2-dimethyl-3-hydroxypyride-4-one (L1) in thalassemia major (TM) : pharmacokinetics, safety and iron excretion. *Blood* Suppl 1990; 76 : 277.
20. Hider RC, Singh S, Porter JB et al. The development of hydroxypyridin-4-ones as orally active iron chelators. *Ann NY Acad Sci* 1990; 612 : 327-338.
21. Kontoghiorghes GJ. The study of iron mobilization from transferrin using alpha-ketohydroxy heteroaromatic chelatores. *Biochim Biophys Acta* 1986; 869 : 141-146.
22. Kontoghiorghes GJ, Bartlett AN, Hoffbrand AV et al. Long term trial with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1) I. Iron chelation and metabolic studies. *Br J Haematol* 1990; 76 : 295-300.
23. Kontoghiorghes GJ, Aldouri MA, Sheppard L et al. 1,2, dimethyl-3-hydroxypyrid-4-one, an orally active chelator for treatment of iron overload. *Lancet* 1987; 1 : 1294-1295.
24. Kontoghiorghes GJ, Goddard JG, Bartlett AN et al. Pharmacokinetic studies in humans with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one. *Clin Pharmacol Ther* 1990; 48 : 255-261.
25. Matsui D, Klein J, Hermann C et al. Relationship between the pharmacokinetics and iron excretion pharmacodynamics of the new oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one in patients with thalassemia. *Clin Pharmacol Ther* 1991; 50 : 294-298.
26. Mehta J, Singhal S, Chablani A et al. L1-induced systemic lupus erythematosus. *Indian J Hematol Blood Transf* 1991; 9 : 33-37.
27. Olivieri NF, Koren G, Freedman MH et al. Rarity of systemic lupus erythematosus in patients taking L1. *Lancet* 1991; 337 : 924.
28. Agarwal MB, Vishwanathan C, Gupta SS et al. Antinuclear antibody positivity in multi-transfused thalassemia major. *Indian Pediatr* 1992; 29 : 607-610.
29. Editorial. Oral iron chelators. *Lancet* 1989; 1 : 1016-1017.
30. Kontoghiorghes GJ, Bartlett AN, Hoffbrand AV. Prospects for effective oral iron chelation therapy in man with 1,2-dimethyl-3-hydroxypyrid-4-one and other alphaketohydroxypyridines. In : *Advances and Controversies in Thalassemia Bone Marrow Transplantation and Other Approaches.* New York : Alan R. Liss Inc. 1989; 107-114.