ORIGINAL ARTICLE

Combined Oral and Parenteral Iron Chelation in Beta Thalassaemia Major

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Summary

Thalassaemics in Malaysia are poorly chelated because desferrioxamine is too expensive and cumbersome for long term compliance. The efficacy and tolerability of the oral chelator deferiprone, and the effects of using a combination therapy in our patients were studied. Ten patients completed the study and the mean serum ferritin reduced from 7066.11 ug/L (2577 - 12,896 ug/L) to 3242.24 ug/L (955 - 6120 ug/L). The liver iron concentration did not show a significant drop (19.6 vs 18.2 mg/g dry weight) although 3 patients showed reductions ranging from 30-40%. Concomitant use of desferrioxamine increased the urinary excretion from a mean of 13.66 mg/day to 27.38 mg/day. Main side effects seen were nausea and rashes.

Key Words: Iron chelation, Thalassaemia, Deferiprone, Desferrioxamine

Introduction

Thalassaemias are hereditary blood disorders indigenous to tropical and subtropical regions of the world where malaria is common. In Malaysia they present a public health problem, as the total estimated number of children suffering from this condition is around 5000[1]. Beta thalassaemia mainly occurs among the Malays and Chinese of West Malaysia, where the gene frequency is around 3%[2]. In beta thalassaemia, the most severe form of thalassaemias, the disease manifests in early childhood; the treatment is 2-3 weekly red blood cell transfusions throughout life. One of the problems associated with this treatment is the accumulation of iron in the body. Excess iron results in multi-organ failure and eventual cardiac death. The accumulation of iron can be prevented by the life long use of the iron chelating agent desferrioxamine mesylate. The drug is expensive. Its use (parenteral only) is cumbersome, painful and many patients find life long compliance difficult, so that life expectancy is around 80% at 30 years of age[3]. Desferrioxamine treatment is only available for a few in Malaysia because of its costs and therefore the life expectancy of Malaysian children with beta thalassaemia not on chelation therapy currently is not more than teenage years, with a sharp increase in death after the age of 10 years.

The only other iron chelator (given orally) which has been tried in long term clinical trials is 1,2 dimethyl-3-hydroxy pyrid-4-one (Deferiprone, L1, Kelfer and Ferriprox). Ferriprox is licensed in Europe for the treatment of iron overload in patients with thalassaemia major, for whom desferrioxamine is contra-indicated, or who presents serious toxicity with desferrioxamine therapy. Kelfer is licensed for the treatment of thalassaemia major in India, whilst the oral iron chelator remains unlicensed in many other countries of the world. Because desferrioxamine is only available in limited quantities in Malaysia, we have started a preliminary study with Deferiprone and a combination of Deferiprone and desferrioxamine in a small group of

children with beta thalassaemia, regularly transfused and grossly iron overloaded. In this case series of 10 patients, we present the results of the iron chelation therapy.

Materials and Methods

Eleven transfusion-dependent patients with beta thalassaemia major were studied (Table I). Ten patients completed the study, one stopped after one month of treatment because of gastro-intestinal problems. All but 1 patient received regular blood transfusions during the trial (Table I). Deferiprone was administered on an out-patient basis in doses of 75-85mg/kg/body weight daily. At each visit compliance was monitored by checking that patients had used up their previous supply of medicine and only a sufficient amount of drug was given until the next appointment. Seven patients received, in addition to daily Deferiprone, subcutaneous infusions of desferrioxamine, given by a constant rate of infusion 1-2g over 8 hours 2 days a week (Table I).

During the 12 month trial period no dietary restrictions were made. Follow up consisted of weekly clinical examination for the first 4 weeks, then fortnightly for

Table I
Patients' Profile

Case	Sex/Age	A	B	C	D	E
1	F/9	8.2	8.4	244	75	1
2	M/9	8.5	9.7	233	80	2
3	F/8	7.8	8.9	226	75	2
4	M/25	7.7	9.6	nil	80	nil
5 •	M/12	9.1	9.4	223	85	1
6	F/6	8.8	8.4	255	75	nil
7	M/8	8.2	8.6	294	75	2
8 *	M/9	7.9	8.6	237	75	nil
9	F/6	8.8	9.7	253	75	2
10	F/14	8.7	8.9	317	85	4

**non -compliant*
•hepatitis B positive
A= Mean pre-transfusion Hb g/dl 2 years prior to the trial
B= Mean pre-transfusion Hb g/dl during trial
C= Mean annual blood consumption ml/kg body weight during trial
D=Deferiprone dose mg/kg body weight
E= Desferrioxamin e dose g/week (given over 8 hours 2 days of weekend)

Table II
Changes in Serum Ferritin and Liver Iron

Case	Initial serum ferritin ug/L	Final serum ferritin ug/L		Initial liver iron mg/g/dry weight	Final liver iron mg/g/dry weight	
1	2578	311	↘	9.85	11.85	↗
2	6527	2535	↘	10.14	10.01	→
3	7415	3165	↘	20.85	22.11	↗
4 *	12,897	1487	↘	29.85	20.70	↘
5 *	6439	5786	↘	27.74	19.85	↘
6	3254	955	↘	18.54	23.32	↗
7	11,132	6120	↘	19.50	18.70	↘
8	8176	4172	↘	18.39	24.82	↗
9	5028	4788	↘	11.14	12.51	↗
10 *	7213	5266	↘	30.08	18.31	↘

Difference between initial and final Ferritin: p=0.007
** = patients with significant reduction of liver iron concentration*
↘↗→ = reduced , increased or no change

Table III
Comparison of Cost between Desferrioxamine and Combination Therapy

Case	Weight kg	DFO chelation at doses recommended by WHO (RM/month)	Chelation costs costs during this trial (RM/month)	Savings %
1	22	859	490	44
2	26	1410	576	59
3	18	1042	444	57
4*	50	2512	900	64
5	23	1287	520	61
6*	19	737	402	45
7	23	1288	560	54
8*	25	1349	394	57
9	22	1226	496	60
10	36	1900	768	60

**not injecting desferrioxamine in combination with deferiprone*
#1 vial DFO 500 mg = RM 15.30
1 capsule deferiprone 400 mg = RM 2.70
(bought by the British pound at the height of the economic crisis)
Cost of injections + Tegaderm +Emla=RM186/month

a further 4 weeks, then 4-weekly until the end of the trial. Clinical side-effects were carefully monitored, in particular, musculo-skeletal and gastro-intestinal complaints. Full blood counts were tested at each visit, liver function and renal function tests were done monthly by standard techniques. Serum ferritin was measured 2-3 monthly by the microparticle enzyme immunoassay (MEIA) method using the Abbot Axsym Immunology analyser. Twenty-four hour urinary iron excretion studies were done at the start of the study. Liver tissue was obtained by percutaneous liver biopsy for histological assessment and for quantitative liver iron estimation by the method of Barry and Sherlock at the beginning and at the completion of the study. Deferiprone was supplied by Vitra, now Pfertec, (Clavering, Essex, UK) Pharmaceutical Company. The study was approved by the Ethical Committee of the Ministry of Health, Malaysia. Written informed consent was obtained from each patient or parents on behalf of the child. Statistical tests for significance was carried out using the student's t -test for paired samples.

Results

In all 10 patients there was a fall in serum ferritin after 12 months of treatment. The reduction was 48% (p=0.007). The reduction was most marked for the single non-transfused patient, whose serum ferritin at the start of the study was 12,897 ug/L, and after 12 months of Deferiprone treatment without desferrioxamine, it dropped to 1487 ug/L. In all patients the mean liver iron concentration was 19.6mg/g dry weight at the beginning of the trial and after 12 months of treatment the reduction was to 18.2 mg/g dry weight only, (statistically not significant). However 3 individuals (cases no. 4, 5, 10) showed significant reduction in liver iron concentration, of which 2 patients were on 85mg/kg body weight of Deferiprone and desferrioxamine 1-4g infused over 8 hours 2 days per week, and one did not receive any blood transfusions (Table II). One patient, case no. 5 had a concomitant Hepatitis B infection and this patient has shown little change in his serum ferritin. However the liver iron concentration has come down in this patient from 27.74 mg/g dry weight to 19.85 mg/g dry weight. Urinary iron excretion studies aimed to compare iron excretion with Deferiprone and desferrioxamine. The combination therapy was found to increase the urinary iron excretion in 7 patients from 13.66 (6.43-32.67) mg/day to 27.38 (11.12-53.36) mg per day. (Figure 1). The cost of this trial was compared with the theoretical costs of chelation with desferrioxamine alone at the recommended doses, and this showed savings of 45-64% for patients (Table III).

Liver histology was evaluated at the beginning and at the end of the trial. All patients had varying degrees of liver fibrosis already present at the start of the trial. Liver fibrosis deteriorated in 1 patient only but the second liver biopsy was only obtained 4 months after stopping the trial, during which period she did not receive any iron chelation at all. Clinical side effects were present in 5 patients. These were mainly nausea and a skin rash associated with mild abdominal discomfort. However, the symptoms were not severe enough to cause ill effects or necessitate discontinuation of the drug. The rash in nature was maculopapular,

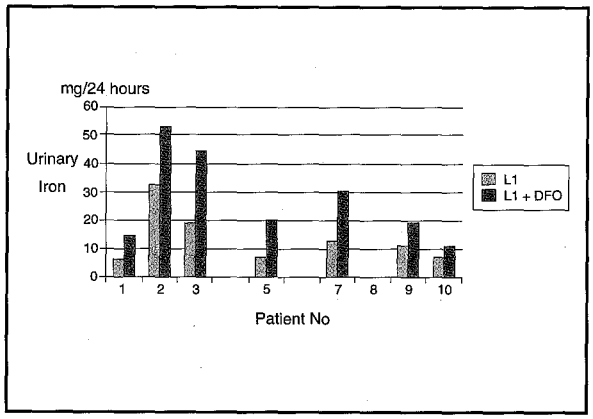

Figure 1: Comparison of 24 Hour Urinary Iron Excretion

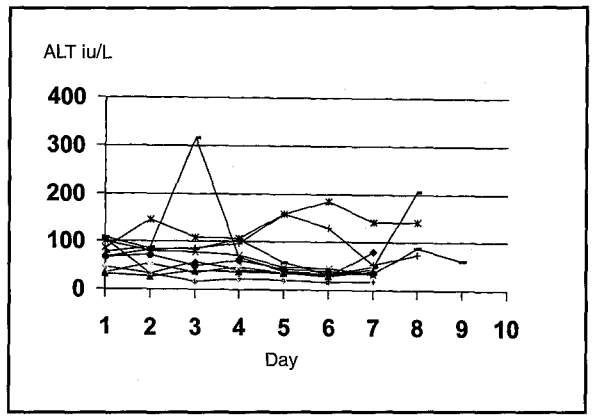

Figure 2: Alanine Transaminase Levels During Trial

pruritic and mainly in the axillary regions, finger webs and neck. It resolved spontaneously with the assistance of mild steroid topical preparation, leaving residual hypo-pigmentation. Serum zinc levels were not assessed in these patients. There was no change in white cell counts or renal function. There was a slight fluctuation in liver enzyme levels. The serum alanine transaminases fluctuated between 2-3 times normal for two patients during the trial, but normalised by the end of the trial. (Figure 2).

Discussion

This pilot study suggests that in Malaysia, where thalassaemic children are not in a position of receiving 'optimal therapy' recommended by WHO[4] can improve their iron chelation using either Deferiprone alone in doses of 75-80 mg/kg/daily or in combination with desferrioxamine 1-2g given over 8 hours two days a week. Although the duration of the study was short and only 10 patients were treated, there was a statistically significant improvement in the serum ferritin levels and no deterioration in the liver iron estimations or in liver fibrosis. Marked falls in liver iron were only observed in 3 of our patients, of which 1 was untransfused. The explanations for this may be that a longer treatment time is needed to lower iron levels and the mean transfusion haemoglobin levels improved by a mean of 0.6g indicating a better transfusion protocol during the trial. Deferiprone in doses of 75mg/kg/day can maintain serum ferritin levels in thalassaemia patients, balancing iron output from transfusions by iron excretion in the urine. This dose has also been shown to maintain liver iron at <15mg/g dry weight in majority of patients with thalassaemia major[5].

Our patients were quite severely iron overloaded at the start of the study. Therefore it was surprising that these 10 patients with very high serum ferritin levels and moderately severe liver fibrosis already at the onset of the study, remained free of side-effects, especially arthropathy, agranulocytosis and gastro-intestinal toxicity. Bartlett et al encountered first the above mentioned side-effects when Deferiprone was given in doses of 100mg/kg/day and Agarwal et al observed more severe arthropathy in Indian patients with initial high serum ferritin levels [6,7]. In our study the dose of Deferiprone was never higher than 85mg/kg/day, and with the combination treatment no arthropathy was observed. The cause of arthropathy in iron overloaded thalassaemia patients treated with Deferiprone remains unexplained. The suggestion that 2:1 or 1:1 complexes of Deferiprone with iron may be formed in the joints and this leads to free radical generation, remains hypothetical, although Deferiprone enters the joints as well as other body fluids. In a earlier study done by Wonke et all, combined therapy using deferiprone at 83mg/kg/day with desferrioxamine infusions at a dose of 4g over 48 hours each week was found to reduce serum ferritin substantially after 6 to 12 months, suggesting an improved method for effective iron chelation, while

potentially reducing costs of desferrioxamine therapy [8]. Grady et all has proposed a "sink" and "shuttle" relationship between deferiprone and desferrioxamine to explain their synergistic effect on iron excretion[9]. Deferiprone, with a partition coefficient more than 20 times greater than that of desferrioxamine, served to shuttle iron from various tissue compartments to the latter hexadentate "sink" confined largely to the bloodstream and the hepatobiliary tract. The bioefficiency of the system is increased while minimising formation of metabolically active complexes.

The reduction in frequency and dosage needed for subcutaneous infusions of desferrioxamine is an advantage in improving compliance. In Malaysia, more than 2000 patients with thalassaemia are regularly transfused and very few receive iron chelation, so most die before reaching their teenage years[10]. As the combination therapy is effective, well tolerated and cost effective, all these children's lives could be raised to the standard of developed countries, where thalassaemics lead a near normal existence and where life expectancy is 'open-ended'. Furthermore, many Malaysian children suffer from haemoglobin E/beta thalassaemia. Most of these children are iron overloaded, although untransfused. In these children low doses of Deferiprone, 50mg/kg/day can reduce iron overload and may improve the quality of their lives [11].

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