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Intravenous and Subcutaneous Desferrioxamine Therapy in Children with Severe Iron Overload

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Abstract. Ten children with transfusion dependent anemias (thalassemia, sideroblastic anemia, congenital pure red cell aplasia) received either intravenous desferrioxamine (DF) in increasing doses up to 450 mg/kg at the time of transfusion or daily subcutaneous DF up to 110 mg/kg on an outpatient basis. No patient on intravenous DF reached a negative iron balance. All children with a subcutaneous DF dose of more than 60 mg/kg obtained a negative iron balance with a *net* iron excretion (transfusion iron already substracted) between 206 to 810 mg (mean 496 mg) monthly. The effectiveness of regular subcutaneous DF on liver storage iron could be confirmed in 4 patients by liver biopsy, showing a decrease between 40–60% iron after 12–14 months of chelation therapy. So far the daily iron excretion has remained constant with a given dose of DF over a period up to 15 months. Even if poor compliance in some patients is taken into account, it is possible with this method of treatment to prevent further accumulation of iron in chronically transfused children.

Key words: Thalassemia – Hemosiderosis – Desferrioxamine – Liver storage iron – Ferritin

Introduction

Organ damage caused by iron overload is the main cause of morbidity and eventually death in patients with thalassemia major and other refractory anemias treated by regular blood transfusion. Heart failure, liver fibrosis and endocrine disorders become manifest after 20 to 60 g of iron has been accumulated [3]. Desferrioxamine (DF) is the most widely employed drug for iron removal. However, given by the intramuscular route a single daily dose very often does not achieve negative iron balance, especially in younger patients [11]. Recently several authors have advocated the use of intravenous or subcutaneous DF as a more efficacious way of removing iron in chronically transfused patients [4, 6, 12, 13].

The objective of our study was to compare the effectiveness of intravenous DF given in increasing doses at the time of transfusion with daily subcutaneous DF in an outpatient programme in children with hemosiderosis. The optimal subcutaneous dose for each individual patient was also determined by progressive increments in the dose of DF and the effect on liver storage iron was evaluated.

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Patients and Methods

Ten patients (age 4 to 18 years) were admitted to the study. Six patients had thalassemia major, two sideroblastic anemia (one congenital, the other evident from 4 years of age) and two congenital pure red cell aplasia (Blackfan-Diamond). Table 1 shows the transfusion iron load, serum ferritin and quantitative liver iron measured by liver biopsy in these patients. The transfusion iron was computed from the iron content of transfused erythrocytes: iron received = packed red cells (ml) × 0.76 [18]. Three patients with thalassemia were splenectomized. Since 1976 all patients were maintained at hemoglobin levels above 9 g/dl).

Intravenous Desferrioxamine. Between 1976 and 1978 intravenous DF was given over 24 h at the time of transfusion in 5 patients. The dose of the drug was increased up to 450 mg/kg in one patient. Blood pressure and heart rate were monitored at 4 h intervals. Twenty-four hour urine collections during the 24 h DF infusion were assayed for iron by atomic absorption spectrophotometry. No patient received ascorbic acid.

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Table 1. Clinical data in 10 patients with hemosiderosis before subcutaneous desferrioxamine therapy

Clinical Data in 10 Patients with Haemosiderosis before s. c. Desferrioxamine

Patient	Diagnosis	Age (yrs)	Transfusion iron load (g)	Serum Ferritin (ng/ml)	Liver Iron (g/kg dry weight)
CA	Thalassemia	4	3,2	-	15,4
TS	Thalassemia	4	12,0	4 500	28,7
NL	Thalassemia	5	6,0	2 700	34,7
HM	Sideroblastic anemia	5	4,4	-	Cirrhosis
NA	Thalassemia	8	17,0	3 393	12,0
BE	Thalassemia	10	10,7	1 210	38,4
RC	Sideroblastic anemia	11	15,5	1 272	13,6 X
MG	Thalassemia	11	23,9	4 072	-
MN	Pure red cell aplasia	16	7	2 011	20,0
ZG	Pure red cell aplasia	18	39,6	3 044	21,0

X) After 16 months of s. c. desferrioxamine

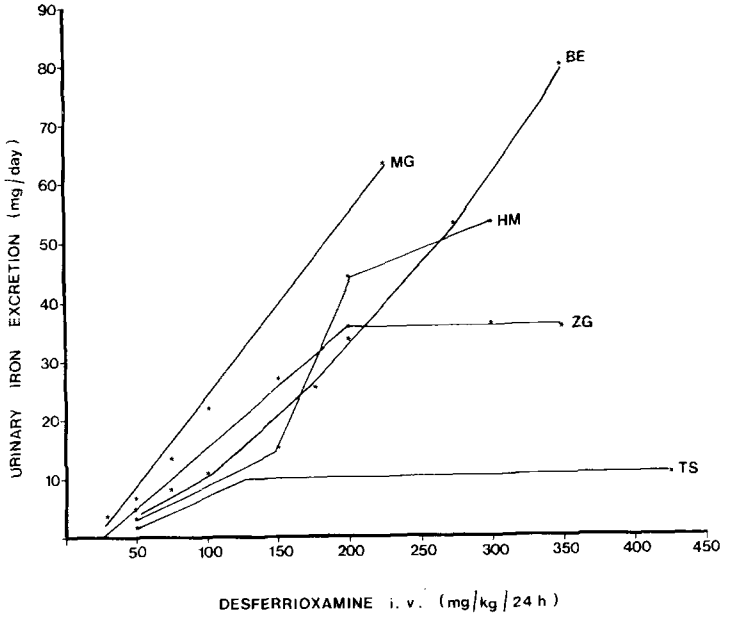

Fig. 1. Urinary iron excretion with intravenous desferrioxamine infusions over 24 h

Subcutaneous Desferrioxamine. Since November 1978 nine patients received subcutaneous DF using a portable infusion pump (Autosyringe, Hooksett, N.H. U.S.A.) starting at a dose of 20 mg/kg DF and increasing stepwise up to a maximum dose of 110 mg/kg—or a total dose of 3 g—dissolved in 10 cc of sterile water. The subcutaneous infusion was done on an outpatient basis, the medication being given over 10 h during the night. Parents were instructed how to dissolve the drug, insert the small 25 gauge butterfly needle, and operate the pump. Most children preferred either the lower arm or upper leg as infusion site. Urine was collected over 24 h 1 to 2 times weekly. Liver samples[1] and urine were assayed for iron as described above. Serum ferritins were measured by radioimmunoassay. At the time of transfusion complete blood counts, liver enzymes and serum values for calcium, phosphorus, copper and magnesium were measured. Screening for hepatitis B virus infection was done every 6 months. Electrocardiograms and more recently echocardiograms were obtained at 4 to 6 months intervals. Patients were advised to visit an ophthalmologist every 6 months to check for cataracts.

Three patients were on medication with ascorbic acid at the start of the study. In others a daily dose 200 mg ascorbic acid p.o. was added at a DF dose of about 80 mg/kg.

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Results

Intravenous 24 h desferrioxamine resulted in a urinary iron excretion up to 90 mg/day (Fig. 1). In two patients

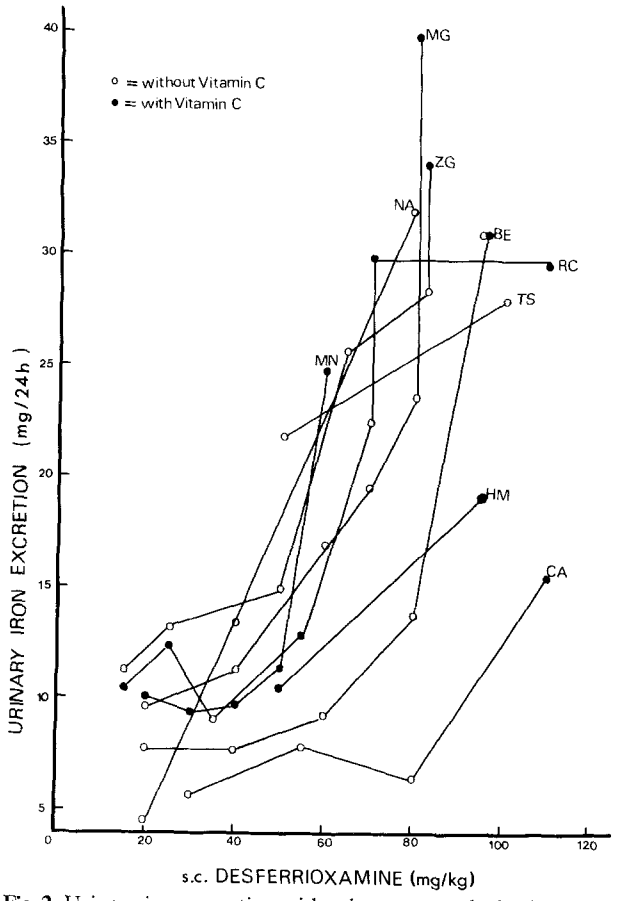

Fig. 2. Urinary iron excretion with subcutaneous desferrioxamine infusions in increasing doses over 10 h

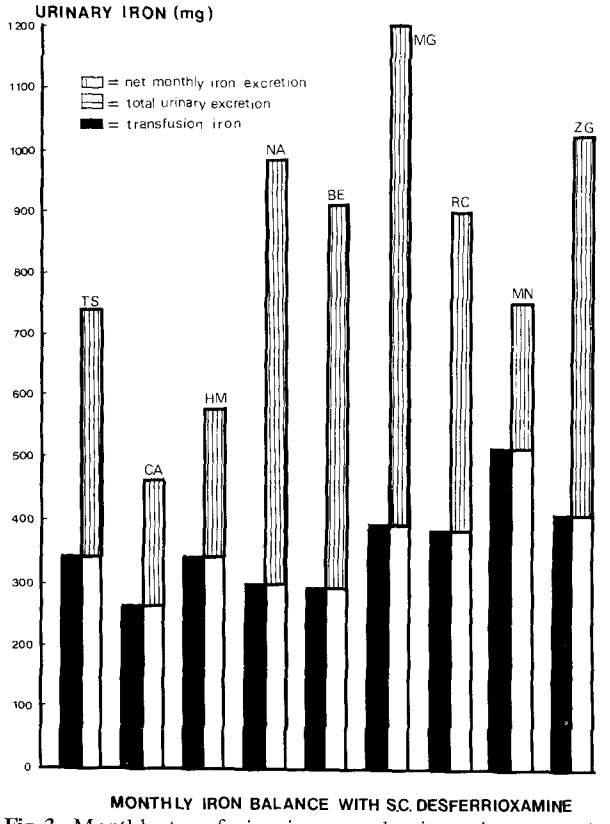

Fig. 3. Monthly transfusion iron, total urinary iron excretion and *net* monthly iron excretion (i.e. total urinary iron excretion minus transfusion iron) assuming daily subcutaneous desferrioxamine therapy

Table 2. Daily urinary iron excretion (mg) and daily transfusion iron load (mg) in patients with subcutaneous desferrioxamine therapy

Patient	Urinary iron (mean ± 2 SD)	Transfusion iron (mg/day)	Desferrioxamine mg/kg
C. A. *	15 ± 5	9	110
H. M. *	19 ± 7	11	95
N. A.	32 ± 0	10	80
B. E. *	30 ± 12	10	95
M. G. *	40 ± 14	13	80
R. C. *	30 ± 8	15	70
M. N. *	25 ± 6	17	60
Z. G. *	34 ± 4	14	80
T. S.	28 ± 15	11	100

* patients with ascorbic acid

a plateau was reached after 130 and 200 mg/kg DF respectively. Since all patients received at least two units of packed red cells every 4 to 8 weeks (equivalent to 400 mg iron), no patient reached a negative iron balance with this type of treatment. No undesired side effects were encountered.

In patients on subcutaneous DF, urinary iron excretion could be increased by stepwise increases in the dose of the drug (Fig. 2). All patients in this study with a DF dose 60 mg/kg or more achieved a negative iron balance, that is, the mean daily urinary iron excretion exceeded the mean daily iron uptake by transfusion (Table 2). If DF was given on a regular daily basis between 206 to 810 mg (mean 496 mg) of iron was removed monthly in addition to the amount of iron given by transfusion (Fig. 3). Supplemental vitamin C increased the daily urinary iron excretion between 20% and 69% in 4 patients and had no effect in another patient.

No serious toxicity was observed. Local problems included burning at the site of infusion and blisters if the needle was not inserted deeply enough. One episode of local skin infection was observed. All children developed some degree of skin pigmentation and induration at the site of infusion. Local irritation was never severe enough to interrupt the treatment for a long time and could be ameliorated with hydrocortisone added to the infusion. The main problem in our patients was the disturbance of sleep with the infusion pump for older children and the fear of the

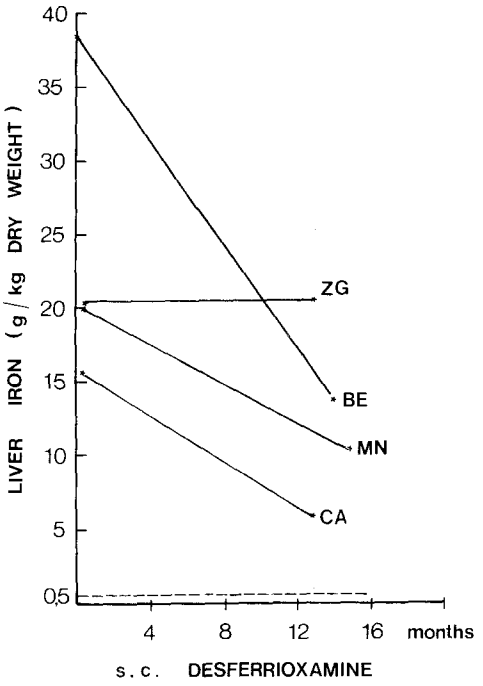

Fig. 4. Change of liver iron assessed by liver biopsy in 4 patients with subcutaneous desferrioxamine therapy

daily needle insertion in younger, rather than local problems.

Monthly determination of copper, magnesium, calcium, phosphorus, liver enzymes and creatinine revealed no abnormalities. One patient in the study had a positive titer against hepatitis B virus surface antigen: in the other children screening for hepatitis B infection gave consistent negative results.

In 4 children the liver was re-biopsied after 12 to 14 months of subcutaneous desferrioxamine therapy. In 3 patients quantitative liver iron decreased by between 40 to 60% of the initial liver iron content (Fig. 4). One patient (Z.G.) showed no decrease. This patient had an average daily iron uptake of 14 mg by transfusion and had only excreted 14 mg of iron with DF doses up to 50 mg/kg. An increase of DF to 70 mg/kg 3 months before the liver biopsy increased the daily urinary iron excretion to 26 mg.

Discussion

Desferrioxamine is thought to act by chelating iron from a labile pool in cells of the reticuloendothelial system [5]. The urinary excretion rates reported underestimate total iron excretion rates because 30–50% of the mobilized iron is excreted in the stool [1]. Moreover, 24 h urine collections for assessment of iron excretion are probably inadequate when considering the prolonged plasma clearance of ferrioxamine which is

Table 3. Compliance with subcutaneous desferrioxamine therapy. Net monthly iron excretion was calculated by subtracting the transfusion iron from the amount of iron excreted in the urine

Patient	Net monthly iron excretion	
	possible excretion (mg) with daily DF	actual excretion (mg)
C. A.	206	106
H. M.	236	198
B. E.	616	473
M. G.	810	- 64
R. C.	519	59
M. N.	230	1
Z. G.	615	496
T. S.	500	471

thought to be due to active reabsorption by the kidneys [16]. Thus the true iron excretion may have been higher, especially in our patients with intravenous infusion of DF and urine collection only once a month. It has been well established that ascorbic acid enhances the effect of intramuscular and subcutaneous DF in patients with iron overload [6, 17]. An increase in urinary iron excretion between 24–245% has been reported [6]. None of our patients on the intravenous DF treatment had ascorbic acid. However, even if all these factors are taken into account it seems highly unlikely that any of our patients could have reached a negative iron balance if DF had been given intravenously only at the time of each transfusion.

In contrast, the subcutaneous DF administration proved to be a very efficient way of removing not only the amount of iron given with each transfusion but also additional storage iron: This could be confirmed by liver biopsy in 3 patients. The net monthly iron removal achieved in our patients was between 206 to 810 mg if DF was given daily. Gastrointestinal absorption of iron should not have played an important role in our patients since hemoglobin levels were kept above 9 g/dl. Also the DF-induced iron excretion in the stools was omitted from the calculation. Since about one third of the chelated iron appears in the stools [1], the net monthly iron removal must be estimated to be even higher. If the monthly amount of iron removed remained constant, theoretically the body iron burden could be reduced by 2.4 g to 10 g a year. So far the effectiveness of DF has remained constant in our patients over an observation period of up 15 months which was also true in another study [13]. However, it seems reasonable to assume that less iron will be removed when the body iron stores are reduced. More-

over, these optimistic figures do not take into account the fact that compliance with this form of treatment is poor in some patients. Since all our parents were asked to keep a record sheet on which the days "on the pump", the duration of the infusion, the urine collections and medications were noted, we were able to calculate the actual monthly amount of net iron excretion for each individual patient. For this purpose the mean daily iron excretion in the urine was multiplied by the number of days on which the infusion pump was used. Although 5 patients still showed a good negative iron balance, in 3 others with poor compliance the results were disappointing considering the possible maximum amount (Table 3). This shows the importance of daily therapy and the need for continuous motivation of patients and parents.

Since desferrioxamine is an expensive drug we tried to determine the optimal dose for each patient. So far a plateau has been reached in one patient only (Fig. 2), but not in all patients has DF been increased to 3 g. In contrast to the results published by Graziano [4], a dose above 20 mg/kg in patients 10 years of age or less further increased urinary iron excretion in 3 of our patients (Fig. 2, patients C.A., B.E., H.M.). The efficacy of subcutaneous desferrioxamine might also be improved by longer infusion times. Hussain et al. found a significant increase in urinary iron excretion when DF (1.5 g) was given over 24 h instead of 12 h [6]. Other investigators reported no change with 20 mg/kg DF infused subcutaneously either over 8 or 16 h [4]. This question was not studied in our patients; to enable normal daytime activities the infusion was limited to 10 h.

It has been shown that serum ferritin concentrations reflect body iron stores [7, 9] and that there is a correlation between the units of blood transfused and serum ferritin levels in patients with hemosiderosis [8]. A recent study in patients with thalassemia challenges these statements [2]. Although our number of patients is small, from our data no good correlation between transfusion iron, serum ferritin and liver iron can be found at the beginning of DF therapy (Table 1). However, in the individual patient ferritin levels decreased between 17%–86% after 5 to 24 months. There also was a good correlation between the decrease in serum ferritin levels and the decrease in liver iron, as well as total body iron. Total body iron was calculated monthly by substracting the actual amount of iron excreted by giving DF from the transfusion iron load at that time.

It is still too early to determine the long-term beneficial effects of subcutaneous desferrioxamine. The critical question remains unanswered as to whether cardiac iron will be removed as well as liver iron. Some preliminary observations about beneficial effects on cardiac function and survival, however, give reason for optimism [10, 15]. Finally, chronic subcutaneous DF treatment remains cumbersome and costly. Although this form of therapy is certainly very effective for iron removal, it remains limited to the few countries which can afford expensive medical treatment. In many countries with a large number of thalassemic patients where the problem of a sufficient supply with blood products has not yet been solved, therapy with subcutaneous DF is out of question. This is also true for other approaches in preventing rapid iron accumulation in chronically transfused patients, such as transfusion of young red cells [14]. Further research to develop an effective oral agent for chelation therapy certainly seems warranted.

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