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Desferrioxamine in Thalassaemia*

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Children with thalassaemia major may be kept alive by repeated blood transfusion. Even then they may die later from intractable cardiac failure, liver cirrhosis, or diabetes mellitus, due to excess deposition of iron in various organs (Engle, 1964). Venesection, repeated at frequent intervals, was tried many years ago to overcome this difficulty. Despite its beneficial effects, venesection imposes a severe strain on the already anaemic patient. Attempts to reduce the amount of iron absorbed by the intestine proved a failure (Moeschlin, 1962). The use of ion exchange agents is not without danger since they eliminate other metals as well as iron (Cleton *et al.*, 1961).

Recently desferrioxamine, a substance belonging to the siderochromes, was found to bind iron; and a hundred parts of it can bind 9·3 parts trivalent iron by weight. The resulting ferric complex ferrioxamine is hardly absorbed from the gastro-intestinal tract. This complex has a molecular weight of 613 and can pass easily through the kidney (Bickel *et al.*, 1960). Desferrioxamine has been used in an attempt to reduce iron deposit in several diseases associated with iron accumulation, and the results on the whole suggest a beneficial effect (Bannerman, Callender, and Williams, 1962; Nielsen, 1963; Wohler, 1963; Moeschlin and Schnider, 1963; Santos and Pisciotta, 1964). Few references, however, are available on the effect of desferrioxamine on renal excretion of iron in thalassaemia (Sephton Smith, 1962; Bannerman *et al.*, 1962; Wohler, 1963).

We have studied the effect of desferrioxamine on iron excretion in 13 cases of thalassaemia major in children.

Material and Methods

Thirteen children with thalassaemia major syndrome were chosen for the present study. They included 12 girls and 1 boy. Their ages ranged from 1½ to 12 years, with one exception who was 17. All showed typical clinical, haematological, and biochemical features of thalassaemia. Two patients were designated as advanced or moderately severe, according to the duration and severity of the disease. Advanced cases were those children with a history of repeated blood transfusions at monthly intervals or more frequently, for the last 2 years. Moderately severe cases were those who either gave no history of blood transfusion or had less than one blood transfusion every 6 months for the last 2 years. 24-hour urine excretions were analysed for iron content 2 days before starting therapy, to determine the average daily iron output. The urine was washed with concentrated sulphuric acid and the iron content of the decomposition solution was determined colorimetrically using α, α-dipyridyl (Keberl, 1964). Since the optimal dosage for desferrioxamine* has not been established, the drug was originally administered intramuscularly in a dose of 500 mg. daily. This proved to give very low renal iron excretion figures. The dose was later increased to 1000 mg. daily in two 12 hourly 500 mg. doses. This gave appreciably higher iron excretion figures and was the dose used for all patients throughout the study. Desferrioxamine was administered for a period of 5 days consecutively. Urinary iron content was estimated daily during this period, as well as on the 6th and 7th days after desferrioxamine had been discontinued. Serum iron and unsaturated iron-binding capacity (Ramsay, 1958) were estimated in all cases immediately before and after the 5-day course of desferrioxamine (except in 3 cases).

Hb, reticulocyte counts, and bone-marrow samples were done just before and 2 days after stopping the therapy in 6 cases.

Results

Table I shows the urinary excretion of iron (mg./24 hours urine) before, during, and after desferrioxamine therapy. Patients are separated into 2 groups —advanced and moderately severe. Significant difference in iron excretion between the two groups is evident.

Table II shows the serum iron and unsaturated iron-binding capacity before and after therapy with desferrioxamine.

Fig. 1 and 2 illustrate diagrammatically the effect

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TABLE I

24-hour Urinary Iron Excretion (mg.) Before, During, and After Desferrioxamine

Case No.	Age (yr.)	Sex	Urinary Iron Excretion Before	Urinary Iron Excretion During					Urinary Iron Excretion After	
				1st day	2nd day	3rd day	4th day	5th day	1st day	2nd day
				Moderately Severe Cases						
1	3½	F	0·252	0·468	0·468	0·936	0·468	0·468	0·188	0·188
2	8	F	0·91	1·05	0·42	2·52	0·189	1·96	1·61	0·42
3	1½	M	1·74	2·14	4·8	4·8	5·0	5·76	4·6	2·98
				Advanced Cases						
4	11	F	0·441	2·38	2·59	2·45	2·73	2·17	0·35	0·35
5	8	F	0·36	0·648	0·696	2·478	2·04	2·06	0·90	2·04
6	4	F	0·40	1·6	1·2	2·12	2·28	2·72	0·92	0·588
7	3½	F	0·42	1·23	2·19	2·79	1·29	2·52	0·45	0·33
8	17	F	2·1	4·4	6·0	7·5	7·2	7·2	4·9	2·6
9	10	F	0·588	1·26	2·45	8·19	1·54	5·6	1·26	1·26
10	2½	F	0·22	0·6	1·68	1·0	1·6	0·54	0·46	0·6
11	12	F	2·4	13·3	13·4	14·08	12·0	7·5	1·97	1·07
12	5½	F	0·86	10·7	6·0	7·9	7·0	6·7	1·24	0·35
13	12	F	0·44	2·0	1·8	2·0	1·8	2·0	1·3	0·55
Mean			0·85	3·21	3·36	4·52	3·47	3·65	1·54	1·02

TABLE II

Serum Iron and Unsaturated Iron-binding Capacity Before and After Administration of Desferrioxamine

Case No.	Age (yr.)	Serum Iron (μg./100 ml.)		Unsaturated Iron-binding Capacity (μg./100 ml.)	
		Before Desferrioxamine	After Desferrioxamine	Before Desferrioxamine	After Desferrioxamine
1	3½	185	—	145	—
2	8	120	105	99	50
3	1½	153	247	81	38
4	11	80	133	127	77
5	8	220	—	44	—
6	4	156	225	85	135
7	3½	263	376	127	—
8	17	185	210	60	21
9	10	288	321	9	9
10	2½	183	—	107	—
11	12	254	305	55	4
12	5½	251	400	56	22
13	12	163	217	51	19

of desferrioxamine on serum iron excretion in two illustrative cases with a small and very large iron excretion. The levels of serum iron and iron-binding capacity before and immediately after the 5-day course of desferrioxamine are also shown.

Bone-marrow and reticulocyte response to desferrioxamine was followed up in 6 patients (Table III). Hb levels before and after therapy are also given.

Discussion

Our results show that in children suffering from thalassaemia major, desferrioxamine in a dose of 1·0 g. daily results in a maximal daily increase of renal excretion of iron varying between 2·8 to 14-fold the original iron excretion values. It is to be noted that maximal iron excretion usually occurred in most cases on the third day or later after therapy, suggesting a slight cumulative effect of desferrioxamine. Withdrawal of the drug resulted in a rapid drop of urinary iron values to almost pre-treatment levels within 48 hours of its discontinuation. Unexplained fluctuations in urinary iron excretion during desferrioxamine administration were occasionally observed. The few previous reports on the effect of desferrioxamine on iron

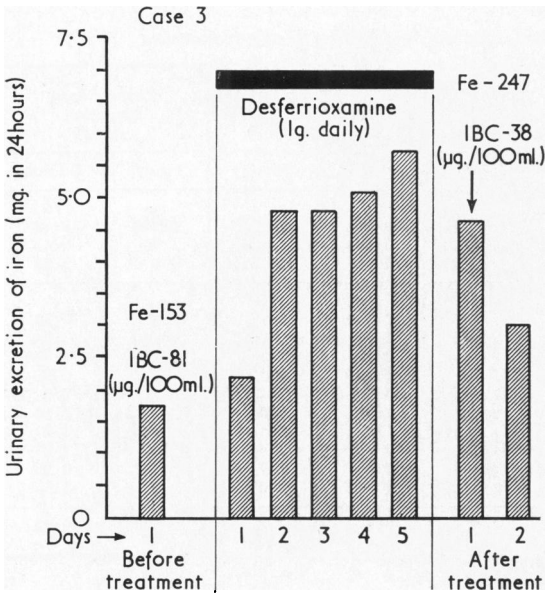

FIG. 1.—*Effect of desferrioxamine on serum iron excretion in Case 3.*

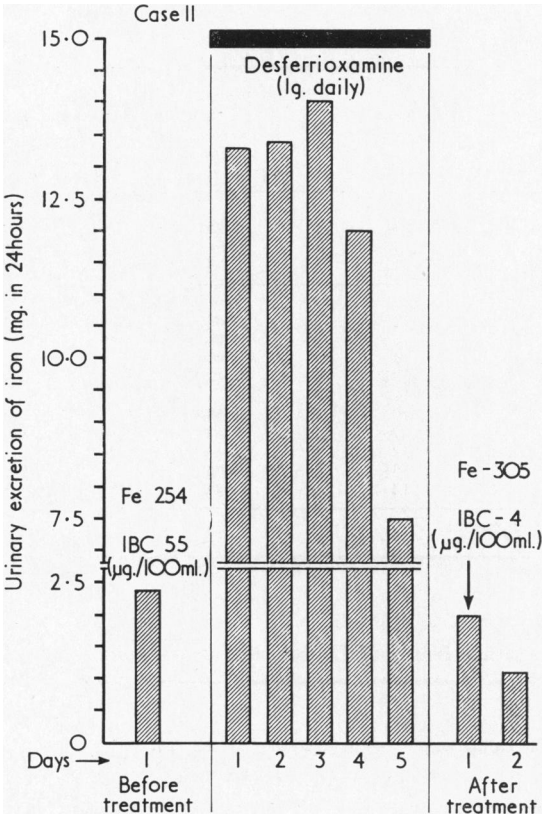

FIG. 2.—*Effect of desferrioxamine on serum iron excretion in Case 11.*

excretion in thalassaemia major gave slightly higher excretion figures than those observed in the present study (Bannerman *et al.*, 1962; Wohler, 1963). This might be related to the fact that most of these cases were older children with a higher iron load. It is evident from Table I that desferrioxamine is more effective in advanced cases with a greater iron load.

The effectiveness of the drug in minimizing iron deposition, with its sequelae in thalassaemia major, is difficult to decide without long follow-up studies on individual cases. As shown in Table I, the mean maximal excretion figure for urinary iron under desferrioxamine was 4·52 mg./day (on the 3rd day); this would amount to 135 mg./month. Most of these children, however, receive on the average 500 ml. blood monthly, with an average iron content of 250 mg. (50 mg./100 ml. blood) (King and Wootton, 1956). It is thus evident that even with maximal efficiency and daily desferrioxamine administration iron output still lags behind iron intake. This is even more pronounced if oral iron

TABLE III

Reticulocytic Response and Bone-marrow Biopsy Before and After Desferrioxamine

Case No.	Before Desferrioxamine			After Desferrioxamine		
	Hb (g./100 ml.)	Reticulocytes	Bone-marrow (M : E ratio)	Hb (g./100 ml.)	Reticulocytes	Bone-marrow (M : E ratio)
1	3·3	0	1 : 3·5	3·5	2·0	1 : 0·8
2	6·0	1·5	1 : 3·5	6·1	10·0	1 : 5·0
3	4·1	0·3	1 : 4·0	4·6	11·0	1 : 10·0
6	6·0	0·5	1 : 3·5	5·5	0·1	1 : 5·0
7	6·0	0·5	1 : 5·0	6·5	5·0	1 : 8·0
13	7·0	2·0	1 : 3·5	7·0	1·8	1 : 4·5

intake in the diet is taken into consideration. Oral absorption of iron is not affected by intramuscular desferrioxamine administration (Stevens *et al.*, 1962). However, until more effective chelating agents or other ways of eliminating iron are available, the use of desferrioxamine is indicated in all cases of thalassaemia in an attempt to minimize the iron overload to which these patients are subjected. Intravenous infusion of larger doses at the time of each blood transfusion might be more effective in iron elimination. The slight risk of the development of cataract following prolonged therapy with desferrioxamine necessitates periodic ophthalmic screening.

Since desferrioxamine liberates iron from iron stores, a temporary rise in serum iron, with lowering of iron-binding capacity, is to be expected immediately after therapy. This was seen in most of our cases. The same observation was also noted by Wohler (1963).

An important observation in the present study is the reticulocyte response observed in 4 out of 6 patients followed up after desferrioxamine administration in the presence of similar haemoglobin levels. This reticulocyte response was associated with evidence of increased normoblastic reaction of the bone-marrow (Table III). That desferrioxamine is a substance possessing oxidative properties has been reported by Wohler (1963), who also thought that it had some effect on the synthesis of haem in achrestic anaemia. He mentioned that this paralleled the excretion of iron promoted by desferrioxamine. He suggested that the improved haem synthesis was secondary to elimination in the urine of some iron compounds that block the active sulphydryl group of enzymes involved in the synthesis of haem. Whether this postulate is correct or not, these preliminary results should stimulate long-term follow-up studies of that aspect.

Summary

Desferrioxamine (an iron chelating agent) was given to 13 cases of thalassaemia in order to evaluate its efficiency in eliminating iron. The results show that 2·8 to 14-fold increases of urinary iron excretion followed a 1 g. daily dose of desferrioxamine. The chelating agent was more effective in long-standing severe cases with a greater iron load. Desferrioxamine was observed to cause a reticulocytosis associated with increased haemopoietic response of the bone-marrow in 4 out of 6 patients studied. It is concluded that until more effective iron-eliminating agents are available, desferrioxamine should be administered to all cases of thalassaemia.

Addendum

After preparation of this manuscript, McDonald (1966) published a report on the effect of desferrioxamine in 4 cases of thalassaemia major. His excretion figures were slightly higher than ours for the 2 long-standing cases, and lower than ours for the 2 younger children. He did not report or comment on any reticulocyte response after desferrioxamine.

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