Deferoxamine and diethylenetriaminepentaacetic acid (DTPA) in thalassemia

Deferoxamine (Desferal) and diethylenetriaminepentaacetic acid (DTPA) were used in 4 children with thalassemia major and increased the urinary excretion of iron in all of them. The best results were obtained in the children with the greatest iron overload. Therapy was less successful in a baby who had not yet accumulated much iron. This form of treatment is thought to be worthwhile as there is, at present, no other practical means of increasing iron output in thalassemic patients.

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THALASSEMIC children who live within reach of a hospital should not die of anemia or infection, but they may die from iron overload, a consequence of the many blood transfusions which their hemolytic anemia necessitates. Iron accumulates in various parts of the body, including the heart, where heavy deposition in the myocardium may ultimately result in cardiac failure. Autopsy studies on such patients have shown large amounts of iron-containing granules in the myocardium, as well as fibrosis and destruction of cardiac muscle.[1] As only small amounts of iron are normally excreted from the body, any increased elimination should benefit thalassemic children. While venesection is the quickest way of ridding the body of excess iron, this is not possible in patients with thalassemia or other hemolytic anemias. The only other method available is the use of preparations which bind iron in the body in an excretable form. Two effective iron chelating agents are deferoxamine (Desferal*) and diethylenetriaminepentaacetic acid (DTPA†). We have had the opportunity of administering each of these preparations to 4 children with thalassemia major and the purpose of this article is to report the results obtained.

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THE PATIENTS

Case 1. This boy, E. I., has been known to us since he was 8 years old. His parents and only brother are well; his sister is the second patient in this group. He presented in 1957 with symptoms of anemia, an increase in fetal hemoglobin and a decrease in the osmotic fragility of the red cells. His parents had hematologic evidence of the thalassemic trait, and a diagnosis of thal-

*Supplied by Ciba Pharmaceutical Company.

†Supplied by Geigy Pharmaceuticals.

assemia major was made in the child. Blood transfusions were given as required and when the intervals between these had shortened to 4 weeks in 1960, his spleen was removed. Since then he has needed blood every 8 weeks. When chelation was commenced in 1964 it was estimated that the boy had received about 16 Gm. of iron by blood transfusions. At this time his liver and heart were both appreciably enlarged. The hemoglobin was 4.3 Gm. per 100 ml. and the peripheral blood smear contained many nucleated red cells. The bone marrow showed erythroid hyperplasia. Serum iron was 220 μg per 100 ml. with 79.7 per cent saturation. Details of treatment are given below.

Case 2. R. I., the sister of the first patient, was seen with her brother in 1957. Her illness has followed a similar course and as her signs are very much like the boy's they will not be described. By April, 1964, she had received about 15 Gm. iron by blood transfusion and chelation therapy was commenced at that time.

Case 3. A. J., a 6-year-old boy, had been pale since the age of 4 months. When first seen by us at 9 months of age, his hemoglobin was 7 Gm. per 100 ml., the liver and spleen were both enlarged, and a systolic cardiac murmur was heard. His red cell survival time was considerably shortened with a half-life of only 15 days. Despite splenectomy at 15 months, blood transfusion was necessary every 6 to 8 weeks. In 1964, when he was 7 years of age, his fetal hemoglobin was 5.3 per cent and there was some decrease in osmotic fragility of the red cells. He had received about 8 Gm. iron from the blood transfusions by this time. Deferoxamine was commenced in 1964 and DTPA was given 4 times during 1965. Details of therapy follow later.

Case 4. G. D. is the youngest patient and was born in March, 1964. He was found to be anemic at 4 months of age, and, in our hospital, at 6 months of age his hemoglobin was 6 Gm. per 100 ml.; the fetal hemoglobin was 21.8 per cent and hemoglobin A_2, 3.5 per cent of the total. Both parents have the thalassemic trait. By August, 1965, the baby's intake of iron from blood transfusions was about 1 Gm. During his more recent hospital admissions he has been given deferoxamine and DTPA; the effects of these are shown later.

MATERIAL AND METHODS

Deferoxamine has a strong affinity for trivalent iron with which it combines to form ferrioxamine. The latter has a low molecular weight and is rapidly excreted in the urine. Wöhler,[2] using Fe^{59}-labeled ferrioxamine found that most of it was eliminated within 24 hours. Deferoxamine may be lifesaving in acute iron poisoning,[3-6] but it has also been found useful in chronic iron retention.[7-9] The trisodium calcium complex of diethyelenetriaminepentaacetic acid (DTPA) has also been found of value in chronic iron overload states.[10-13] It has been suggested that calcium is exchanged for iron at storage sites and that the newly formed chelate is then excreted in the urine.[10] Labeling with C^{14} indicated that up to 70 per cent is eliminated from the body within 4 hours and practically all of it is removed by 24 hours.[14]

Neither preparation is effectively absorbed when given by mouth, so that parenteral administration is necessary. Deferoxamine is usually given intramuscularly and only chelates iron. In moderate doses it appears to be nontoxic. There was a report[15] of ataxia, paralysis, and respiratory failure in experimental animals, but they had received excessively large doses of deferoxamine.

As the maximum dose had not been established, deferoxamine was administered in an initial daily dose of 1 Gm. (2 ml.) and increased up to 3 Gm. (2 ml. three times a day). We wished to find out if increasing the dose of deferoxamine would result in a proportionately increased excretion of iron in the urine. Initial increases were not maintained, so the daily dose was reduced to see if a steady output of iron was obtained on a 1 Gm. (2 ml.) dose, this being the dose selected as the most convenient one for outpatient use.

DTPA was given intravenously at the time of blood transfusion, either in the blood itself or in 5 per cent dextrose solution. Dosage varied from 125 to 200 mg. per kilogram and was administered in a dilution of 1 Gm. in 150 ml. diluting fluid, given rather slowly. Intramuscular injection of DTPA is too painful for repeated use. Magnesium as well as iron is eliminated by this agent,[11] and as the serum-magnesium level

tends to be reduced in thalassemia,[16] DTPA should probably not be used too frequently. No toxic effects were apparent in our patients and serum magnesium, as well as calcium levels, were substantially the same before and after chelation on the one occasion when these were measured.

The determination of serum iron and latent iron-binding capacity was carried out under controlled conditions of pH using unbuffered sulfonated bathophenanthroline for color development. Urinary iron was determined by releasing iron from deferoxamine under controlled pH conditions using sodium hydrosulfite as a reducing agent. Thereafter two independent methods were used, employing either dipyridyl or unbuffered bathophenanthroline for color development.[17]

RESULTS

Figs. 1 to 7 show urinary iron excretion after chelation in the 4 patients. Their pretreatment figures for 24 hours were 0.32 mg., 0.44 mg., 0.15 mg., and 0.25 mg., respectively.

The 2 children with the heaviest iron overload had a good response to deferoxamine during three hospital admissions. The amount given was reduced to 1 Gm. (2 ml.) daily during their second and on their third admissions, in order to find out if there was a constant urinary excretion of iron per gram of Desferal. This amount was then given as outpatient treatment to the children on 4 days per week for the next 5 months. Values for urinary iron are not available during the latter period except for 2 periods of 24 hours each when the children were brought into the hospital for random 24 hour urinary iron determinations. From the various values obtained it seemed that 10 mg. iron per gram of Desferal was a conservative estimate of urinary iron excretion for each child. Although it cannot be claimed that this is an accurate value, it is thought it is not too far out as a basis for calculation. After 5 months the estimated output of iron in each child was 900 mg. In the case of the boy, his urinary iron output in the hospital was 630 mg., making a total excretion of iron of 1,500 mg. in 8 months.

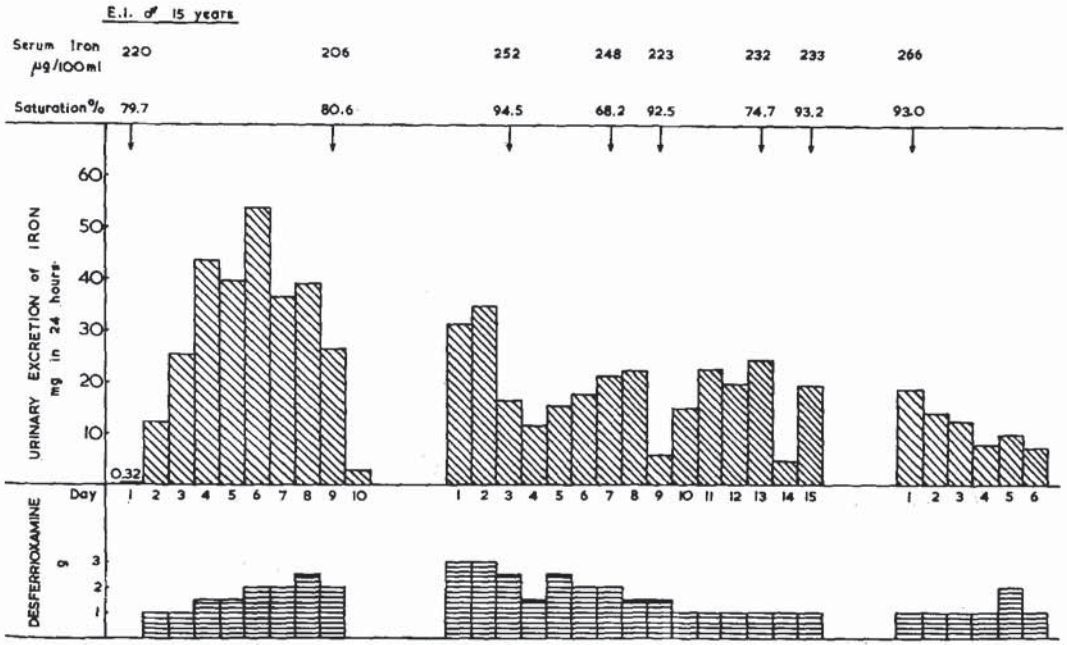

Fig. 1. Iron excretion with deferoxamine. (E. I., 15 years.) Inverted arrows indicate serum iron determinations.

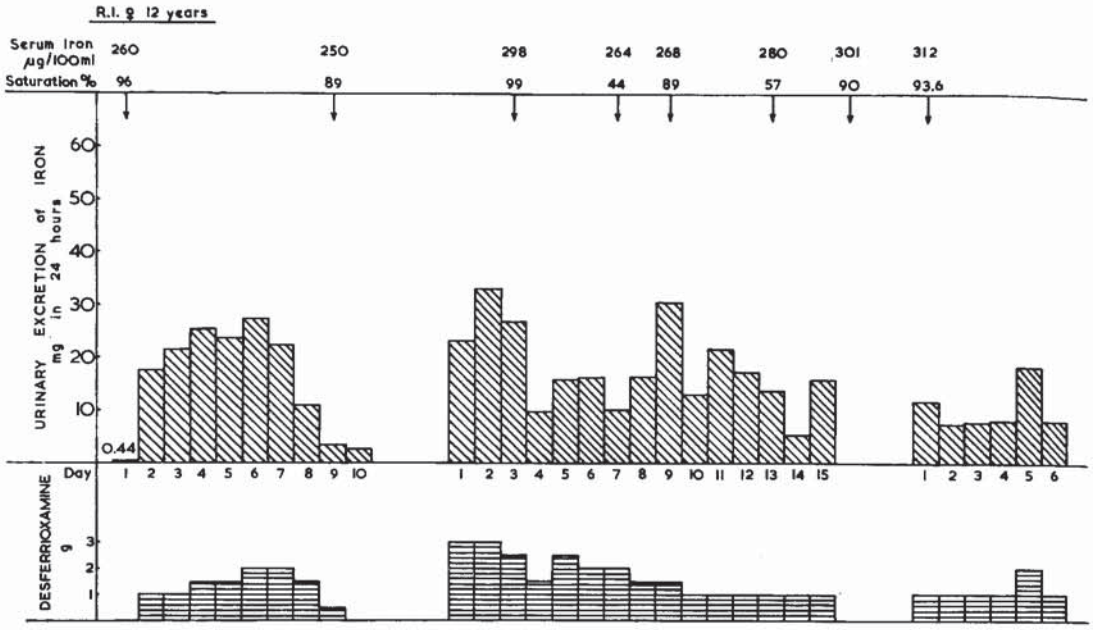

Fig. 2. Iron excretion with deferoxamine. (R. I., 12 years.) Inverted arrows indicate serum iron determinations.

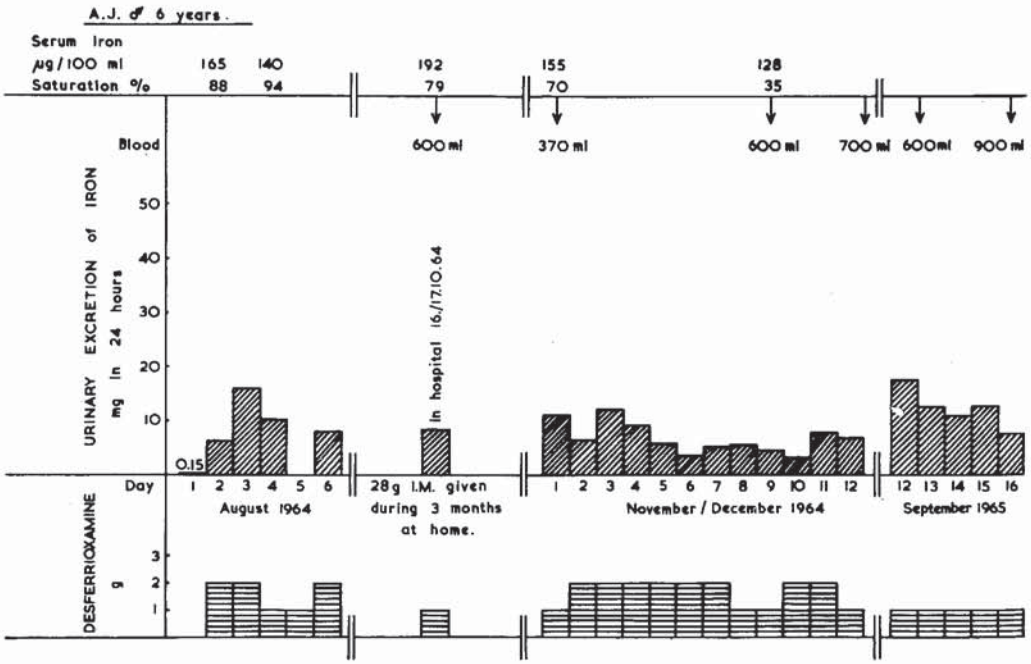

Fig. 3. Iron excretion with deferoxamine. (A. J., 6 years.) Inverted arrows in this and subsequent Figs. indicate blood transfusions.

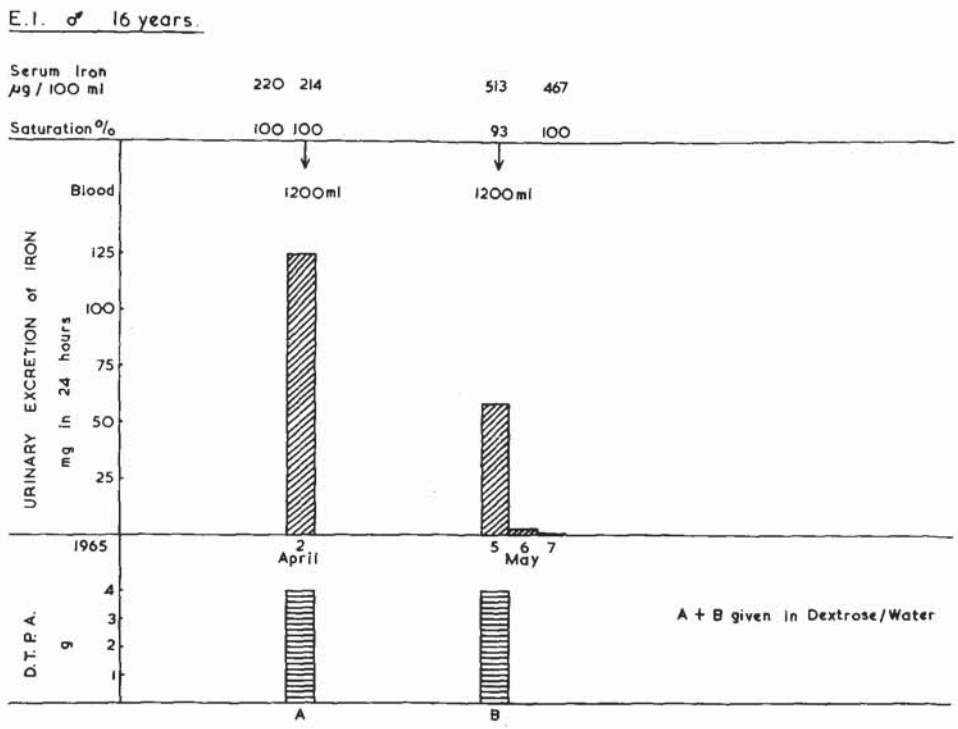

Fig. 4. Iron excretion with intravenous DTPA. (E. I., 16 years.)

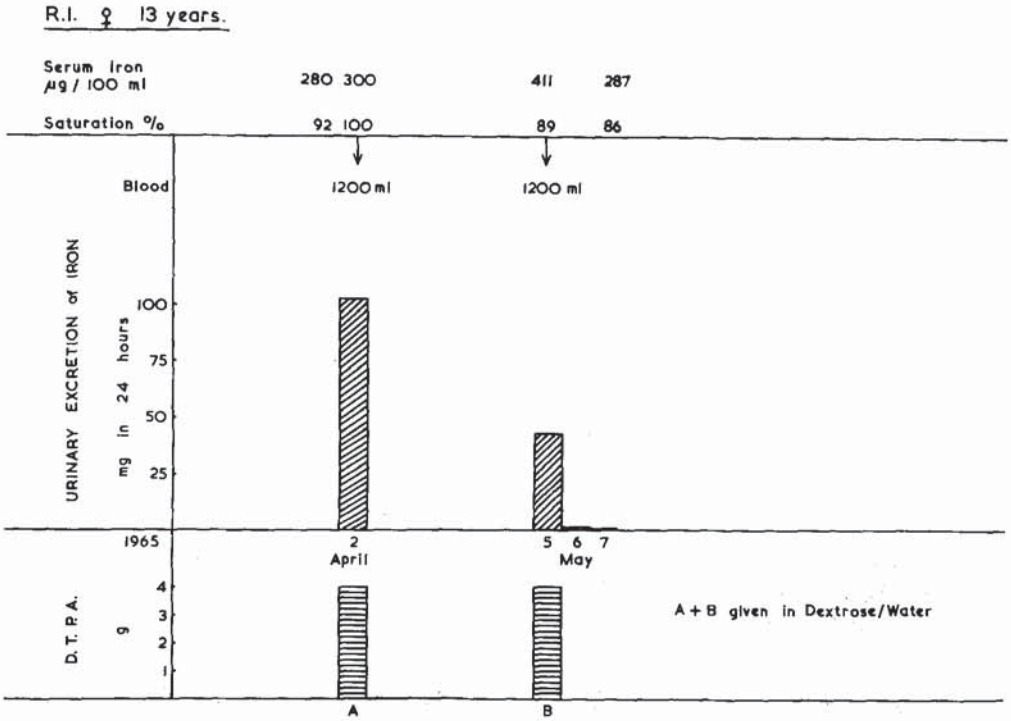

Fig. 5. Iron excretion with intravenous DTPA. (R. I., 13 years.)

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