TREATMENT OF IRON OVERLOAD WITH DESFERRIOXAMINE B*

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TRANSFUSION Siderosis occurs when excess amounts of iron are laid down in the tissues following multiple blood transfusion for non-haemorrhagic conditions.

In diseases such as severe haemolytic, aplastic anaemia, the need is for red cells, but therapy by transfusion supplies not only the required red cells, but also a considerable quantity of unwanted iron.

Sachs et al. (1933) have calculated that 100 ml. of whole blood in man contains from 44-56 mgs. of iron. Finch and Finch (1955) consider that 100 transfusions of 500 ml. of whole blood represents a potentially harmful iron excess. This number of transfusions entails an intake of 25 G. of iron compared with the normal 4 G. of iron in the body.

At present there are two forms of treatment for iron overload, venesection and the use of chelating agents. Venesection is useful in the treatment of idiopathic haemochromatosis, but is not desirable where the underlying problem is one of anaemia. A chelating agent is a substance which competes for and binds closely with metallic ions. When siderosis is due to multiple transfusions for severe haemolytic or aplastic anaemia, only chelating agents can be used to remove iron.

Of the chelating agents available, desferrioxamine B seems the most effective. Others, dimercaprol (B.A.L) and ethylenediamine tertacetic acid (E.D.T.A.) have been employed, but are not specific for iron and do not remove sufficient quantities to justify their use (Ohlsson et al. 1953; Seven et al. 1954). E.D.T.A. does not remove iron from transferrin in rabbit serum, and appears to combine with iron only in those areas of the body where it is in direct competition with the iron binding protein for free ferric or ferrous ions (Rubin, Houlihan and Princiotto, 1960). Diethylenetriamine-penta-acelate (D.T.P.A.) has removed substantial amounts of iron (Bannerman et al., 1962). Penicilline chelates lead and copper but as yet has not been used for iron overload.

Desferrioxamine is produced by removing iron from the growth producing metabolite Ferrioxamine, a coloured compound which has been isolated from the organism streptomyces pilosus. Ferrioxamine, when given intravenously, was found to be excreted rapidly in both anaemic and non-anaemic patients. Sixty per cent. of this substance, unaltered, was excreted in the urine in 24 hours and 90 per cent. in 3 days (Bickel et al., 1960). This demonstrates the firmness of the bond. Desferrioxamine B has been shown by Wohler (1961) to remove iron, in vitro, from transferrin, haemosiderin and ferritin. Bannerman et al. (1962) found that good quantities of iron could be removed in the urine by the use of desferrioxamine B.

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Methods

Desferrioxamine is supplied as a white powder in sealed bottles, each containing 200 mgs. It was dissolved easily in 2-3 ml. of sterile normal saline. Only 5 grammes were available for the present study. This amount was divided into two, to establish the effect following intramuscular and intravenous injection. Two hundred mgs. were given intramuscularly three times a day for four days. Fifteen days later, whilst two 500 ml. bottles of washed packed red cells were being given, 1 gramme of desferrioxamine B was added to the first and 0.6 gramme was added to the second.

Urinary and serum iron estimations were carried out prior to therapy. As no iron could be detected in the urine, a full 24 hours estimation was not carried out. Twenty-four specimens of urine for iron estimation were collected each day during the intramuscular course, and for two days afterwards. Similar specimens were collected during and for 3 days after the intravenous infusion.

The following methods were initially employed to estimate serum and urinary iron.

1. Following Ramsay (1957).
2. A modification of the Ramsay technique.

The method of Ramsay (1957) involves heating the specimen for five minutes with hydrochloric acid, reducing with sodium sulphate and obtaining an optically measurable coloured solution with 2, 2' dipiridyl. The modification, which only differs in that the mixture of specimen and HCL are heated together for 1 hour, was the only method used for the majority of the specimens as it gave the highest yield of iron. These results are comparable with those obtained by Bannerman et al. (1962) using the method of Bothwell and Mallett.

All end solutions were read in 1 cm. cuvettes in a spectrophotometer at 520 mu. Specimens of serum for assay, were undiluted but the urine specimens were diluted 1/5 to bring results into a range below 300 μg/100 ml.

CASE HISTORY: Mr. M. O'D. aged 55 years, who was employed as a dental mechanic, was admitted to the Meath Hospital in February, 1961, complaining of breathlessness and pain in the chest, dry non-productive cough, general weakness and tiredness, paraesthesia in both hands, more marked in the right, swelling of ankles and blurring of vision. All these symptoms apart from breathlessness and pain in the chest had been present for about 2 years. On examination he was pale and anaemic looking, there were no lymph glands palpable and no enlargement of liver or spleen. He was found on ophthalmoscopic examination to have retinal haemorrhages of various types, most of which appeared recent. His blood count on admission was:—Hb. 3.0 gms.%, P.C.V. 11%, MCHC 27%, W.B.C. 2,400/cu. mm., platelets 76,000/cu. mm.

Sternal marrow biopsy and puncture showed a rather hypoplastic marrow with some cellular elements still present, but no malignant cells. Peripheral blood film showed hypochromia, anaerycotosis, poikilocytosis and polychromasia, some macrocytes were seen. Test for occult blood in faeces was negative and a fractional test meal showed achlorhydria. Blood urea was 32 mgms./100 ml. and serum proteins totalled 7.0 gms., electrophoresis showing a slight increase in globulin. The L.E. cell and serological tests performed were negative, the Coombs test was also negative. An osmotic fragility test gave a normal reading, haemolysis starting at 0-44% NaCl. A barium meal x-ray and skeletal x-rays showed no pathological lesions.

Chromium tagging of the red cells was carried out in July, 1961 and showed reduced red cell survival time with no evidence of haemolysis. However, it was thought that