IRON DEFICIENCY ANAEMIA TREATED BY TOTAL DOSE INFUSION OF IRON DEXTRAN COMPLEX

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Anaemia due to iron deficiency is still one of the commonest conditions seen in medical practice today. In the majority of patients a satisfactory response can be expected with oral iron therapy which is the treatment of choice. However, in a proportion of cases because of intolerance to oral iron, or because a rapid response is required, as for example, severe anaemia discovered late in pregnancy, or in the preparation of patients for major surgery, parenteral iron therapy is indicated. This is usually given by the intramuscular route which has certain limitations and disadvantages.

In recent months, a single total dose technique for the administration of iron dextran complex—Imferon has been described, Basu (1963), Powell (1963), Lane (1964), Gartlan (1964), Varde (1964), and Basu (1965).

The lack of toxicity of iron-dextran complex, Martin et al (1955) has allowed its safe administration as a single total dose infusion (T.D.I.) accurately calculated to provide a rapid and complete correction of the patient's iron deficient stores.

This paper describes the experience and results obtained with an initial trial with total dose infusion of iron dextran complex in 50 patients.

CLINICAL MATERIAL

The trial was carried out on a total of 50 patients with proved iron deficiency anaemia. The diagnoses of the patients were as follows:- postpartum anaemia 26 cases, sixteen of whom were complicated by haemorrhage; antepartum anaemia of pregnancy 19 cases; and two cases each of anaemia due to abortion, chronic menorrhagia associated with uterine fibroids and malnutrition with hookworm infestation.

The period of gestation of the cases with antepartum anaemia were as follows:- between the 25th. to 28th. week 4 cases, 29th. to 32nd. week 6 cases, 33rd. to 36th. week 5 cases, and 37th. to 40th. week of pregnancy 4 cases.

With the exception of one patient with malnutrition and hookworm infestation, all the other 49 patients were females. The age distribution ranged from 16 to 61 years, with the majority (42) being between the ages of 20 to 40 years. The ethnic distribution of the patients were, Chinese 23, Indians 18, Malays 8, Eurasians 1.

HAEMATOLOGICAL METHODS

Following the clinical assessment a full haematological examination including a microscopic examination of the peripheral blood film and an estimation of the serum iron content was carried out for every case. The haemoglobin estimation was carred out on capillary blood by the cyanmethaemoglobin method with an EEL. Hb. meter, standardised against standard reagents obtained from Diagnostic Reagents Ltd. Thames, Oxon.

The serum iron estimation was carried out by the method of Ramsay (1958). All cases had in addition a determination of the hematocrit and the mean corpuscular haemoglobin concentration, MCHC carried out.

The diagnosis of iron deficiency was established by the finding of a hypochromic microcytic type of anaemia, together with a low MCHC and serum iron value. This was often accompanied by the finding on clinical examination of koilonychia and atrophy of the tongue and mucous membranes with stomatitis.

The presence of other types of anaemia which would contraindicate iron therapy was excluded in all cases by a routine Coombs Test and haemoglobin electrophoresis. A marrow examination and other laboratory investigations were carried out when indicated.

All patients were in-patients having been hospitalised for investigation and treatment of the anaemia. None of the patients had received

any form of iron therapy prior to treatment. They were discharged from hospital on the day following the infusion of iron. Patients were then seen and haemoglobin estimations carried out at weekly intervals for four weeks and thereafter at fortnightly intervals for a further four weeks. A repeat serum iron estimation was carried out between the 4th. to 6th. week after infusion of iron.

PROCEDURE for adminstration of Iron by total dose infusion technique.

The requirements of iron dextran complex for each patient were determined by reference to dosage tables provided by the manufacturers. These have been calculated according to the level of haemoglobin and the body weight taking into consideration not only the need to return the haemoglobin level to normal, but also to replenish the body's depleted iron stores. In pregnancy, an additional 10 ml. of iron dextran complex, equivalent to 500 mg.Fe, is added to meet the demands of the foetus and to compensate for blood loss at delivery.

The iron dextran complex is added aseptically to sterile normal saline to give a 5% v/v solution. In practice, 25 ml. of iron dextran complex is added to a 540 ml. (1 pint) bottle of normal saline. Volumes in excess of 25 ml. are added to proportionate amounts in a second bottle.

The infusion apparatus is assembled and venepuncture performed making use of a large vein in the cubital fossa. At the onset, the infusion is run at a slow rate of 10 drops per minute for about 10 minutes, during which time the patient is carefully observed for reactions. If no untoward reactions occur, the rate of infusion is increased to 45 drops per minute, until completion of the full dose. This normally takes an average of 5 to 6 hours. The temperature, pulse, respiration and blood pressure were recorded before, during and at the end of the infusion.

The total dose of iron dextran complex given to the individual patients ranged from 20 ml. (1,000 mgm.Fe) to 55 ml. (2,750 mgm.Fe) with an average dose of 2,000 mgm.Fe.

REACTIONS

No instances of anaphylactic reaction were encountered in the 50 patients. Mild and transient reactions consisting of fever and chills occurred in 3 patients, headache occurred in one, and parasthesia of the limbs occurred in another.

Thrombophlebitis of varying degrees occurred in 21 (42%) of the patients. 13 of these were very mild redness of the vein, 7 patients had redness plus some degree of induration of the vein. All of these did not require any specific treatment and the thrombophlebitis cleared up within a few days. Only one case developed severe thrombophlebitis with extensive redness and induration of the vein with pain which required treatment with analgesics, antibiotics, and hot formentation. This cleared up after 2 weeks.

RESPONSE TO TREATMENT

Haemoglobin Values

The initial haemoglobin values in the 50 patients is shown in Fig. 1. The haemoglobin levels ranged from between 25% to 60% (100% - 14·6 g.) with the majority having haemoglobin levels of 50% or less.

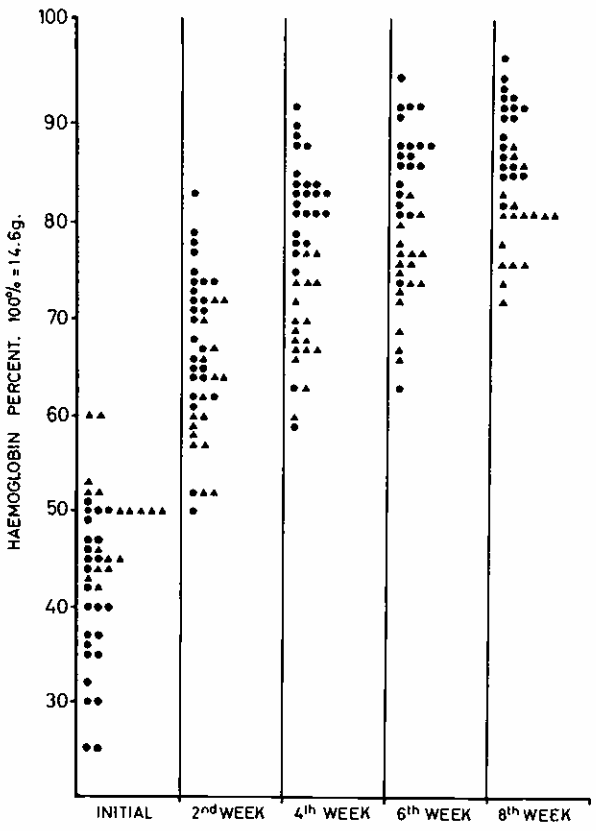

Fig. 1. Showing haemoglobin levels of patients initially, and at 2nd., 4th., 6th. and 8th. week after infusion of iron dextran complex.

● = patients with good response.

▲ = patients with suboptimal response.

Of the 50 patients, 42 were observed for a minimum of four weeks. Eight patients, all cases of postpartum anaemia defaulted and were observed for less than four weeks. They were

not included in the analysis. Of the 42 patients, it was found that 25 (60%), had a very good response with a haemoglobin rise over a four week period of between 31 to 60%. 9 patients (21%), had a suboptimal response with a haemoglobin rise of between 21% to 30%, whilst 8 patients (19%), had a poor response with a haemoglobin rise of less than 20% over the four week period.

A study of the 25 good response cases showed that they had an average rise in the Haemoglobin level in the first two weeks of 30·3%. The average rise in the haemoglobin level between 2nd. and 4th. weeks, 4th. and 6th., and 6th. and 8th. weeks were 11·5%, 4·4% and 2·8% respectively.

The average rise in the level of haemoglobin over the four week period was 41·8% or 1·5 g/100 ml. per week. The average rise in the level of haemoglobin over the four week period in the patients with suboptimal and poor response was 20% or 0·74 g/100 ml. per week.

Serum Iron Values:

The serum iron values before treatment and 4-6 weeks after treatment are shown in Fig. 2.

The initial serum iron values ranged from 17 mcg.% to 84 mcg.% with an average of 48 mcg.%. 4-6 weeks after treatment, the serum iron values ranged from 38 to 201 mcg.% with an average of 100 mcg.%.

31 patients had serum iron values of above 80 mcg.% whilst 11 patients had values below 80 mcg.% after treatment.

Blood Transfusion:

10 cases of postpartum anaemia received a total of 16 pints of blood for severe haemorrhage before the infusion of iron dextran complex. None of them received any blood transfusion after institution of iron therapy. 8 cases of antepartum anaemia received blood transfusion, 6 of them before the infusion of iron because of the very low initial haemoglobin level. Two cases, with poor response had to be given blood transfusion after iron therapy because delivery was imminent and the haemoglobin level was still low.

DISCUSSION

The results of this initial trial are similar to that obtained by earlier workers, Lane (1964), Varde (1964) and Basu (1965).

Following total dose infusion of iron dextran complex there is a very rapid rise in the haemoglobin level which is most marked in the first two weeks after which there is a more gradual rise until the haemoglobin reaches normal levels between the 4th. to 8th. week.

The average rise in the haemoglobin of 1·5 g.% per week is slightly higher than that obtained by Lane (1964) who found a mean haemoglobin rise per week to be 1·03 g.%, Varde (1965)

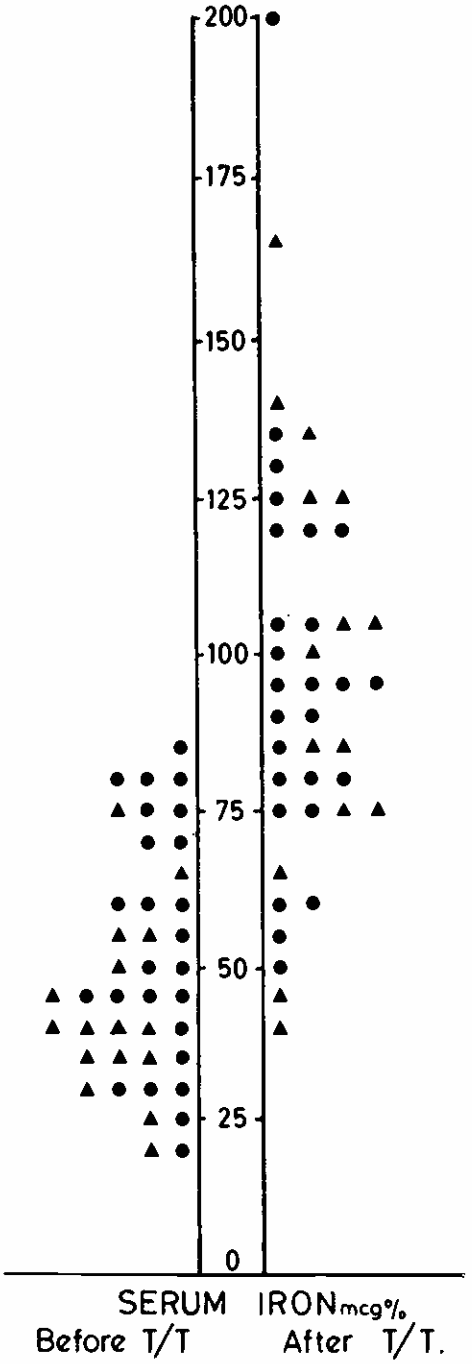

Fig. 2. Showing Serum Iron Values of patients initially and 4 to 6 weeks after infusion of iron dextran complex.
● = patients with good response.
▲ = patients with suboptimal response.

obtained an average rise in haemoglobin of 2% per day in 300 cases of iron deficiency anaemia of pregnancy.

The results also showed that the degree of response was related to the initial haemoglobin level. Thus it can be seen from Fig. 1 that cases with a good response generally tended to have lower initial haemoglobin levels. The mean initial haemoglobin level of good response cases was 40% and that for the suboptimal and poor response cases was 49%. Varde (1964) showed that a patient with an initial haemoglobinl evel of below 50% had an initial haemoglobin rise of about twice that of patients with haemoglobin levels between 50-60% and approximately 4 times that of patients with an initial haemoglobin of between 70-75%.

An analysis of the 17 patients with a haemoglobin rise over the four week period of less than 30% showed that 14 of them were cases of antepartum anaemia and 2 of postpartum anaemia, one case had a persistent severe menorrhagia.

Three of the 17 patients had associated toxaemia of pregnancy, and one had a chronic urinary infection. Five patients responded with small doses of folic acid although a reappraisal of the peripheral blood picture and an examination of the marrow did not reveal any evidence to suggest a megaloblastic erythropoiesis. A concomitant subclinical folic acid deficiency being responsible for a suboptimal response has also been reported by Scott (1963), Basu (1965) and Gartland (1964). Chanarin and associates (1965), made the observation that iron deficiency may conceal the morphological criteria of a megaloblastic anaemia and that iron deficiency in itself produced an additional stress on folate metabolism. Scott (1963) also made the observation that latent folic acid deficiency becomes overt as a result of treatment with iron.

Eleven patients were found to have persistently low serum iron values of less than 80 mcg.%. Following further doses of parenteral iron dextran complex they showed further improvement in the haemoglobin level. The finding of a number of patients with low serum iron values after treatment was rather surprising in view of the large doses of iron administered. 5 of these were patients with a suboptimal response. There were also 6 patients among the good response cases with serum iron levels of less than 80 mcg.% after treatment. Two of these were given iron dextran complex by the intramuscular route and the remining had oral ferrous sulphate.

No apparent cause for the poor response was found in three remaining cases. The observation that 14 out of the 17 cases with suboptimal response were antepartum cases suggests the possibility that haemodilution of pregnancy may be partly responsible. Basu (1965) found an average mean daily rise in haemoglobin of 1·3% in antepartum patients, whereas for postpartum patients the mean was 2·4%.

Anaphylactic reactions have been observed occasionally by earlier workers. In most instances these have occured almost immediately following commencement of the infusion. No instances of anaphylactic reaction were encountered in this series of 50 cases. With the exception of Clay and her colleagues (1965) who observed thirteen reactions out of 150 cases, seven of which were severe and demanded emergency treatment, the majority of other workers have obtained a much lower incidence of reactions. Lane and Scott (1965) give an overall rate of 0·28% out of a total of 1,807 fully documented cases.

About the only reaction encountered to any great extent was a local phlebitis of the infused vein. With the exception of one case which required active treatment, all the others were mild and transient requiring no treatment. The use of normal saline as a dilutent instead of 5% dextrose has been reported to reduce the incidence of thrombophlebitis. The manufacturers have further suggested the possibility of using plastic catheters which if properly placed along the vein ensure a slow flow of iron dextran complex solution right into the centre of the vein, well away from the sides, thereby reducing further the frequency of thrombophlebitis.

The administration of iron by total dose infusion technique has the advantage of certainty of dosage and administration. The dose is determined individually for each patient taking into consideration the need to correct the haemoglobin level and to replenish the deficient stores.

Its advantage over oral therapy is that there is no need for self medication for the patient to ignore or forget and the need for prolonged therapy continuing for several months after the haemoglobin level has returned to normal is obviated.

It has also advantages over intramuscular injections which are very painful and liable to give rise to complications like abscesses, nerve paralysis and staining of the skin over the injection site.

Anaemia in the last trimester of pregnancy often presents a problem in the management. The very rapid hematological response obtained within the first 14 days after infusion has been a tremendous advantage in the treatment of these cases. The same would apply in the case of patients needing to undergo urgent major surgery when time is at a premium. Under such situations, it is not unusual for doctors to resort to the use of blood transfusion which is not without its own risks and hazards. The use of total dose infusion of iron dextran complex in this study has meant a definite saving in the use of blood, a finding which has been well demonstrated by Lane (1964) and Varde (1965).

The one great advantage of total dose infusion technique is that it is much less time consuming for the patient, as well as for the medical and nursing staff. The usual practice has been for patients to come up to the Outpatient Clinic either daily or twice weekly for their intramuscular injections, and in a number of instances patients have defaulted before the course of injection is complete. This advantage is of especial importance to the poor patients where social and economic factors make repeated outpatient visits difficult.

The more severely anaemic patients are usually admitted to hospital for further investigation and for a series of parenteral injections. The average length of stay in hospital for the patient would be anything from 7 to 10 days. Whilst the administration of iron by total dose infusion requires hospitalisation, with experience we have found it possible for patients to be investigated as outpatients following which arrangements are made for them to be taken in as lodgers for the day. Patients are admitted in the morning for their infusion of iron, one hour after completion of the infusion, which is usually in the evening they are ready to leave for home. In this way it has been possible to make available valuable bed space which would otherwise have been occupied with these patients. This is of paramount importance especially in Singapore where the availability of beds is limited and there is a constant need for a rapid turnover of patients.

SUMMARY

50 patients with proved iron deficiency anaemia were treated with iron dextran complex administered by total dose infusion technique.

The technique provides a safe, convenient and rapidly effective means for the correction of iron deficiency anaemia.

The haematological response in 60% of cases was very good with an average rise in the haemoglobin level over the four week period of 1·5 g./100 ml. per week. The causes for the suboptimal response in the remaining 40% of cases were discussed.

There were no serious toxic side reactions except for a mild thrombophlebitis occuring in 21 of the 50 patients. The advantages of total dose infusion technique were discussed.

ACKNOWLEDGEMENTS

I wish to thank the consultant obstetricians of Kandang Kerbau Maternity Hospital for the opportunity to carry out this study on cases under their care.

I wish to thank Messrs. Fisons (Malaya) Ltd. for their generous donation of Iron Dextran Complex—Imferon—used in the trial.

REFERENCES

1. Basu, S.K. (1963): "Rapid administration of Iron Dextran in late pregnancy", Lancet, i, 1,430.
2. Basu, S.K. (1965): "Administration of Iron Dextran Complex by continuous intravenous infusion".
3. Chanarin, I., et al. (1965): "Iron Deficiency and its relation to folic acid status in Pregnancy: Results of a Clinical trial", Brit, Med. J. i, 480.
4. Clay, B., et al. (1965): "Reactions to total doses intravenous infusion of Iron Dextran (Imferon)", Brit. Med. J. i, 29.
5. Gartlan, G.J. (1964): "Parenteral Iron in Pregnancy", Brit. Med. J. i, 435.
6. Lane, R.S. (1964): "Intravenous infusion of iron-dextran complex for iron-dificiency anaemia.", Lancet, i, 852.
7. Lane, R.S., Scott, J.M. (1965): "Reactions to Intravenous Iron Dextran", Brit. Med. J. i, 449.
8. Martin et al. (1955): "The pharmacology of Iron Dextran Intramuscular Haematinic", Brit. J. Pharmacol., 10, 375.
9. Powell, R. (1963): "Iron-Dextran—Total dose infusion Technique", Lancet, ii, 252.
10. Ramsay, W.N.M. (1954): "The determination of Iron in Blood Plasma or Serum", Biochem. J., 53 227.
11. Scott, J.M. (1963): "Iron-Sorbitol-Citrate in Pregnancy Anaemia", Brit. Med. J. ii, 354.
12. Varde, K.N. (1964): "Treatment of 300 cases of iron deficiency of pregnancy by total dose infusion of iron dextran complex", J. Obset. & Gynaec. Brit. Cwlth., 71, 919.