A NEW CARBOHYDRATE-IRON HAEMATINIC FOR INTRAMUSCULAR USE

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In recording the clinical trial of an unsuccessful intramuscular iron preparation (Goldberg and Hutchison, 1953) attention was drawn to the valuable, though limited, field of usefulness of intravenous iron therapy and to the wider applicability of intramuscular iron, could a suitable preparation be elaborated. The desiderata were that the preparation should be an effective haematinic freely absorbed from the tissues and non-irritating. Our recent experience with a new dextran-iron complex ("imferon") has convinced us that it is highly satisfactory for intramuscular use, and we present a preliminary account of our findings.

Methods and Materials

Venous blood was used for all haematological investigations, the anticoagulant being solid potassium-ammonium oxalate mixture (Heller and Paul, 1934). Haemoglobin was estimated by the method of Clegg and King (1942), using a Hilger photoelectric absorptiometer calibrated by crystalline haemin. 100% Hb was taken to be equivalent to 14.8 g. Hb per 100 ml. blood. The packed cell volume was determined by centrifuging the blood at 2,200 *g* for 30 minutes in sealed Hawksley haematocrit tubes.

The intramuscular iron preparation has been administered to two of us and to 15 patients suffering from iron-deficiency anaemia. These patients had haemoglobin values during the control period within the range 29–66% and were judged to be iron-deficient usually on three criteria—namely, low mean corpuscular haemoglobin concentration (M.C.H.C.), low serum iron, and absence of stainable iron in the sternal marrow (Hutchison, 1953). One patient, a woman with severe mitral stenosis, died shortly after treatment began; the cause of death was a massive cerebral embolus from the left auricle. Thus 14 patients have been followed up long enough for assessment of the haematinic effectiveness of the preparation (see Table). Of these 14 patients, 6 were known to be refractory to, and 2 had shown marked intolerance of, ferrous sulphate by mouth.

Before the commencement of treatment the test subjects were kept under observation for from seven to sixteen days, except in the case of one severely anaemic woman whose control period (three days) had of necessity to be short. Her own practitioner, however, vouched for a chronic anaemia of some months' duration in spite of treatment with both vitamin B_{12} and oral iron. During the control period in all cases two to five specimens of blood were examined to ensure that no significant fluctuation in the values was occurring and to provide a base-line by which to measure the effect of the preparation under trial.

Dosage.—The optimum dosage schedule is still under consideration, but 4 ml.—that is, 200 mg.—every other day into alternate buttocks has proved satisfactory; smaller amounts have also proved effective, but have the disadvantage of more frequent administration, and there are indications that response is more rapid when treatment begins with the larger doses. The patient's iron deficit was calculated approximately on the basis that 100 mg. Fe is equivalent to 4% Hb.

Details of Cases

Clinical Summary	Duration of Therapy (Days)	Total Iron Given (mg.)	% Hb		P.C.V. (%)		M.C.H.C.(%)	
			Before Therapy	After Therapy	Before Therapy	Therapy After	Before Therapy	After Therapy
1. F. 60. Achlorhydria. No haemorrhage	130	1,100	66	98	36·6	46·4	26·7	31·3
2. F. 39. No achlorhydria Slight menorrhagia ..	71	1,200	61	88	30·2	42·4	29·9	30·8
3. M. 61. Achlorhydria W.R.+. No haemorrhage	117	1,200	60	87	32·4	41·8	27·4	30·8
4. F. 66. Achlorhydria. No haemorrhage	97*	1,300	52	97	29·9	47·4	25·7	30·3
5. F. 42. Gastrectomy for ulcer in 1950. Menorrhagia	36	1,400	52	80	30·1	41·9	25·6	28·3
6. F. 65. Achlorhydria. No haemorrhage	50	1,400	46	89	28·9	44·6	23·5	29·5
7. F. 38. Menorrhagia ..	27	1,800	31	82·5	20·2	46·0	22·7	26·5
8. F. 43. Menorrhagia. Plummer–Vinson syndrome	47	1,600	37	83	22·2	39·3	24·6	31·2
9. F. 32. Plummer–Vinson syndrome	37	1,600	54	83	32 0	42·3	25·0	29·1
10. F. 62. Achlorhydria ..	55	2,000	31	72	20·5	37·9	22·4	28·1
11. F. 36. Achlorhydria. Menorrhagia	158*	1,800	44	93	26·0	45·0	25·1	30·6
12. F. 32. Achlorhydria. Menorrhagia	50	1,800	45	85	27·5	45·0	24·2	28·0
13. F. 28. Achlorhydria. Plummer–Vinson syndrome	50	2,000	29	76	19·0	44·0	22·6	25·6
14. F. 44. No achlorhydria	25	1,400	48	71	29·3	38·8	24·2	27·1

100% Hb = 14·8 g. Hb per 100 ml.

* In these two cases there was a considerable interval between the tabulated and the previous blood examinations, and the haemoglobin levels were probably reached much sooner than the figures indicate.

Results

Absence of Reactions Following Injection.—In no single instance was the injection followed by any general reaction, and no more than slight local tenderness was ever experienced even when a dose of 5 ml. was administered; in effect the preparation seemed bland and thus provided a striking contrast to preparations of intramuscular iron formerly tried. The serum iron in two instances was found to be sustained at a remarkably high level—for example, 2,860 μg.—for a period of days without any sign of toxic effect.

Haematological Response.—A significant rise in the serum iron content was demonstrable less than 18 hours after the initial injection. The reticulocytes were followed in some cases and showed a slight increase; a patient with 29% Hb initially showed 12% reticulocytes on the sixth day. In every patient a satisfactory rise in the haemoglobin took place. The speed with which this occurred varied, and factors which may be concerned are still under examination, but in general the rate of response was inversely proportionate to the initial haemoglobin level, and is probably to be interpreted as reflecting the degree of cellularity of the marrow. The slowest and most rapid responses are shown in Fig. 1. Over the whole series the average weekly rise in haemoglobin during the first month of treatment varied from 0.51 to 1.67 g. Hb per 100 ml. per week (3.5–11.3% Hb per week). The packed cell volume (P.C.V.) was more rapidly restored to the normal range than the Hb, the

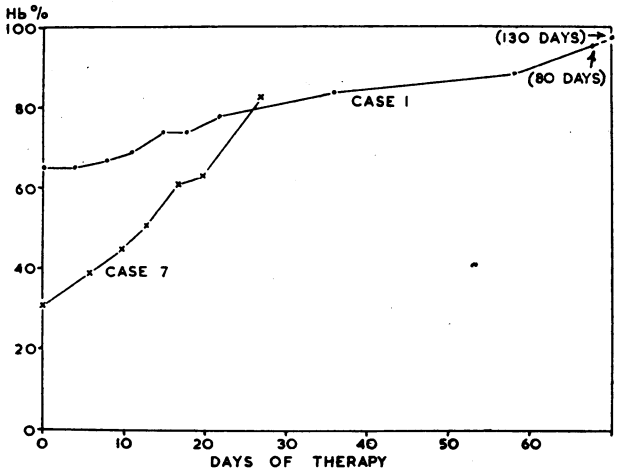

FIG. 1.—Showing variation in rate of haemoglobin response.

effect of this being to delay considerably restoration of the M.C.H.C. In Case 7 this is well illustrated. The Hb has reached a level 1.1 standard deviation short of the mean—that is, just within the normal range (Hendry, 1949), whereas the P.C.V. has exceeded the mean 2.6 S.D. and the M.C.H.C. is still 6.8 S.D. below the mean. In one case examination of the sternal marrow following treatment showed that stainable iron, absent before the starting of treatment, could now be demonstrated in the R.E. cells.

No attempt has been made to assess accurately or in detail the degree of utilization of the iron injected, but from the figures available this seems to be over 80% in some instances.

Discussion

This carbohydrate-iron preparation has been shown to be effective and non-toxic in the treatment of iron-deficiency anaemia. The rate of increase of haemoglobin varied in different cases, but, in general, was greater in young severely anaemic patients than in those beyond middle age with only moderate anaemia. In some patients clinical improvement became obvious within a week of the starting of treatment, while in others it was delayed for two to three weeks, but eventually all the patients in the series developed a vigorous sense of well-being which contrasted very strikingly with their previous chronic ill-health.

Compared with the intravenous iron preparations the new compound has the great advantages of easier administration and lower toxicity, while its therapeutic effect is similar. The only minor drawback was a tendency to staining of the skin in the area of the injection. This developed only in the first two patients treated, and was prevented in the others by injecting 1–2 ml. of air after the solution. The pigmentation appeared within 24 hours of the offending injection in both patients, and in the beginning was thought to be a bruise, but its true nature soon became apparent when, over the succeeding weeks, the colour changed to a slaty-grey, resembling the skin pigmentation of idiopathic haemochromatosis. Pigmentation was still obvious, although less intense, four months after the courses of treatment.

A small piece of pigmented skin was removed for histological examination from one of the patients three months afterwards; iron pigment was abundant in phagocytes in the corium, but melanin in the overlying epithelium was also increased, contributing to the pigmentation. Because of the possibility of skin pigmentation the site of injection should be the buttock and not the upper arm or thigh; this precaution is especially necessary in young females. None of our patients showed evidence of sensitization, either by a reaction during the course of injections or subsequently when the skin was tested with dextran. We have, however, heard of an instance in which urticaria developed immediately following an injection of this iron-dextran preparation (Dr. J. Wallace, personal communication), and the development of sensitivity in some instances is a possibility that should be borne in mind.

Serum total iron estimations proved that absorption took place rapidly from the muscles. The death from cerebral embolism of the cardiac patient provided an opportunity of studying the route of absorption, and at the dissection of the injection sites the application of the prussian-blue reagents to the tissues showed streaks of more intense iron staining in the fat which appeared to mark the course of lymphatics. The regional nodes were faintly brown, and histological examination subsequently (see Fig. 2) demonstrated large amounts of iron in the sinusoidal lining cells. Traces of iron could be seen in the lymph of the afferents outside the gland and also in lymphatics in the skin overlying the injection sites. It was clear from this that absorption was taking place via the lymphatics. When 200 mg. Fe was administered every other day sustained serum total iron levels of the order of 1,500 μg. were produced, but no appreciable loss of iron in the urine was detected.

The indications for the use of this new preparation are strictly limited and are the same as those for intravenous iron—that is, intolerance of or refractoriness to oral iron

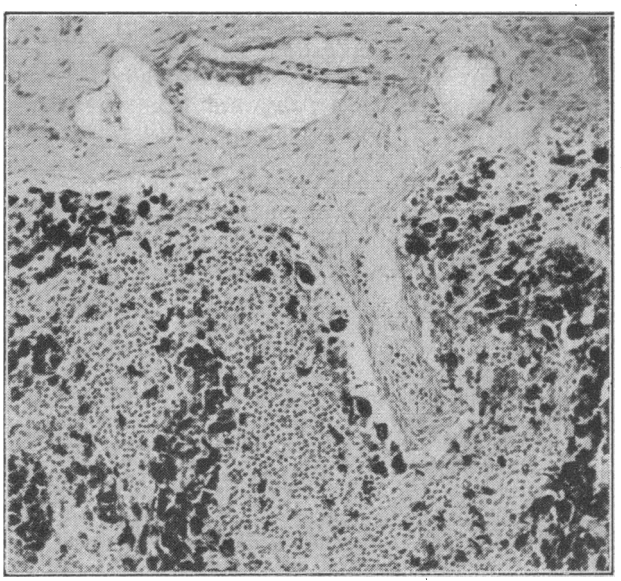

FIG. 2.—Lymph node draining injection site shows sinusoidal lining cells filled with iron. (Prussian-blue reaction. ×125.)

(Ramsey, 1950; Hawkins, Peeney, and Cooke, 1950), or circumstances such as pregnancy (Govan and Scott, 1949; Benstead and Theobald, 1952) or pre-operative preparation (Briscoe, 1952) in which a more rapid response than can be obtained with oral iron is desired. Since this carbohydrate-iron compound is much easier and safer to inject than saccharated iron oxide, parenteral iron therapy may become more popular, especially in general practice, for it ensures that the necessary quantity of iron is made available for haemoglobin synthesis and eliminates the uncertainties inherent in oral administration. Indeed, there is a possibility that it may become too popular. First, intramuscular iron might be prescribed too frequently for patients with iron deficiency who require only iron by mouth, but secondly, and more important, there might be a tendency to give it indiscriminately and in large doses to patients who do not have a deficiency of iron. The long-term effects of parenteral iron overdosage in humans are not yet fully understood, but, although the deposit of moderate amounts of surplus iron in the tissues does not in itself seem to be notably harmful, it is undesirable to administer this or any other parenteral remedy where it is not required. Accurate diagnosis and a proper trial of oral iron should therefore precede the use of intramuscular iron. The provision of an

effective, non-toxic, and easily administered intramuscular iron preparation should not be made an excuse for the indiscriminate use of parenteral iron therapy.

Summary

A preliminary account is given of the successful clinical trial, in 15 patients, of a newly elaborated proprietary dextran-iron haematinic ("imferon"). The agent proved non-irritating when given intramuscularly and was readily absorbed, giving serum iron levels of 600 μg. within eighteen hours; absorption via the lymphatics was demonstrated histologically. The complex proved an effective haematinic, giving average haemoglobin regeneration rates of between 3.5 and 11.3% Hb per week over the first four weeks of treatment.

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ANAEMIA OF PREGNANCY TREATED WITH INTRAMUSCULAR IRON

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The injection of iron intramuscularly as a therapeutic measure is no new procedure. As early as 1893 Stockman recognized the efficacy of this mode of administration, but, as he and subsequent authors (Barlow and Cunningham, 1911; Bullock and Peters, 1911; Witts, 1933; Heath, Strauss, and Castle, 1932) pointed out, the toxicity of the solutions employed was so great that only small quantities could be injected. Consequently, the rate of haemoglobin regeneration was actually less than that found with oral iron therapy. At the same time Heath *et al.* (1932) showed that the utilization of the injected iron for haemoglobin formation was nearly 100%. Fowler and Barer (1937) did not wholly agree with this. They stated that in all their cases the iron was retained, but in three out of four of their patients no improvement in haemoglobin level occurred. It was generally felt that until a less toxic preparation was available there was no real case for the intramuscular administration of iron.

The following is a report on the results obtained by the treatment of iron-deficiency anaemias of pregnancy with a new preparation "imferon" which can be given intramuscularly as well as intravenously.

Materials and Methods

Fifty pregnant women with iron-deficiency anaemia were treated with this preparation. All had haemoglobin values less than 10 g.%* In 14 the anaemia was mild—9 to 9.5 g.%; in 28 the haemoglobin lay between 8 and 8.9%, and in the remainder the anaemia was severe, haemoglobin being less than 8 g.%. All but one had a red-cell count over 3,000,000 per c.mm. This patient had a red count of 2,850,000 with a haemoglobin reading of 5.7 g.%. All were of microcytic hypochromic type with normoblastic marrows. Serum iron levels estimated by the method of Sven Dahl (1948) were uniformly low—from 10 to 65 γ per 100 ml., the average being 35 γ per 100 ml. Four of the patients were treated in hospital; the remainder were out-patients. Initially, two schemes of dosage were employed. Thirteen patients, including the four in hospital, were given daily injections equivalent to 100 mg. of elemental iron. Others received larger doses, representing 250 mg. of elemental iron, twice weekly. Subsequently all patients were treated with the larger dose. This preparation of iron is much more concentrated than the intravenous forms involving the use of the saccharated oxide. Each millilitre contains 50 mg. of elemental iron.

Daily estimations of haemoglobin, haematocrit values, and reticulocytes were made on those patients receiving daily injections. Similar estimations were made at regular intervals on other patients. Each week a complete investigation was made on all patients. Serial estimations of serum iron were made in selected cases.

*68% on the scale of 14.8 g. ≡ 100%.

Results

Daily haemoglobin and haematocrit readings, carried out on those patients receiving the smaller dose, revealed a characteristic pattern of changes somewhat similar to that found in patients treated with intravenous saccharated iron. The haemoglobin rose slightly during the first 24–48 hours. Thereafter a fall occurred, a minimum value being reached by the fourth day of therapy. Subsequently there was a rapid improvement. These sudden initial changes in haemoglobin were probably due in part to variations in blood volume. Curiously, however, the haematocrit reading increased from the beginning and there was a similar increase in mean cell volume. It is likely that these increases were caused by an outpouring of normocytes from the marrow, and this might tend to mask blood-volume changes.

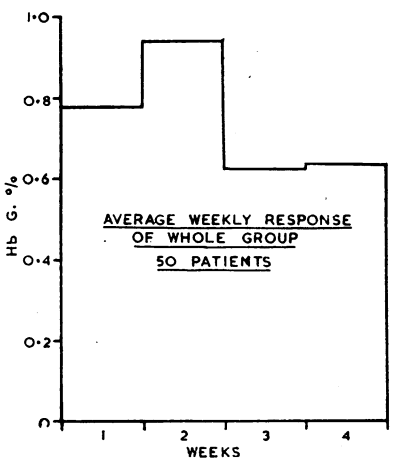

FIG. 1.—Average weekly haemoglobin increments of whole group.

The average haemoglobin increments during the first three weeks following treatment are shown in Fig. 1. During the first week the average increase was 0.77 g.%. The average increment for the whole group during the second week was 0.94 g.%. By the third week many of the cases were almost normal, and the percentage increase for the group was only 0.62 g.%. Study of the cases, however, indicated that, as with all forms of iron therapy during pregnancy, two main types of response were shown. Adopting an arbitrary response of 0.5 g. as a significant figure, it could be shown that, during the first week of therapy, in the greater proportion of patients (42) the haemoglobin increased by 1.1 g. In the remaining eight patients the increase during this period amounted to only 0.22 g. During subsequent weeks the response of both groups was similar. Haemoglobin increments of the two groups are shown in Figs. 2 and 3.