

TREATMENT OF IRON DEFICIENCY ANÆMIA WITH SACCHARATED IRON OXIDE GIVEN BY THE INTRAVENOUS ROUTE*

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PATIENTS with iron deficiency anæmia, refractory to or unable to tolerate iron by mouth, present a difficult therapeutic problem. The search for a safe and effective iron preparation for parenteral use covers many years.¹ Small doses of iron have been given in this way on many occasions. Intramuscular injections were excessively painful and intravenous doses much in excess of 10 mgm. produced severe toxic reactions. Dramatic hæmatologic responses in patients with iron deficiency anæmia have been observed after intravenous infusions of large doses of colloidal iron hydroxide, but severe reactions occurred in every case.² Nissim³ reported the successful treatment of iron deficiency anæmia with large intravenous doses of saccharated iron oxide. His preparation was a variable product but toxic reactions

were less severe than those encountered by earlier workers. Slack and Wilkinson⁴ developed a stable preparation of saccharated iron oxide for intravenous use and recorded the successful treatment of 60 cases of iron deficiency anæmia. No severe toxic reaction occurred although large doses of this material were used.

We are presenting the responses of six patients with iron deficiency anæmia to intravenous injections of saccharated iron oxide. Five were refractory to iron by mouth and one could not tolerate this therapy.

Clinical material.—The salient features of the six patients are shown in Tables I and II. Clinical and hæmatologic studies indicated iron deficiency in each case. In no case did iron deficiency seem to be due to blood loss. Two of the three women were past the menopause and the third had normal menses. Four of the six patients had undergone partial gastrectomy for peptic ulcer; one had cirrhosis of the liver; and one, a chronic alcoholic, had received antabuse for twelve months.

Saccharated iron oxide.—We used three preparations, each of which contained 2% iron. Two, "feojectin" and "ferrivenin", were proprietary products.* The third was prepared by Mr. F. Zahalan, chief pharmacist of the Hospital, according to the method of Slack and

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* Supplies of "Feojectin" were donated for this study by Smith, Kline and French Laboratories. "Ferrivenin" is manufactured by Messrs. Benger's Limited.

TABLE I.
CLINICAL FEATURES

Case number	Age	Sex	Duration (years)	Causative factors	Symptoms						Signs				
					Tiredness	Dyspnoea	Palpitation	Anorexia	Dyspepsia	Dysphagia	Pallor	Glossitis	Angular stomatitis	Koilonychia	Achlorhydria
1	61	F.	20	Partial gastrectomy	+	+	+	+	+	0	+	+	0	+	0
2	42	F.	2	Partial gastrectomy	+	+	+	0	+	0	+	0	+	+	+
3	66	M.	6	Partial gastrectomy	+	+	+	+	+	0	+	+	+	0	+
4	38	M.	½	Antabuse (?)	+	+	0	+	0	0	+	0	0	+	0
5	65	M.	2	Cirrhosis of liver (?)	+	+	+	0	0	+	+	+	+	0	+
6	55	F.	5	Partial gastrectomy	+	+	+	+	+	0	+	+	0	+	

RESPONSE OF 6 CASES TO SACCHARATED IRON OXIDE BY THE INTRAVENOUS ROUTE

TABLE II.

Case number	Before treatment						After treatment (no Oral Iron given)																					
		Days before 1st treatment	R.B.C. (millions per c.mm.)	Hgb. (grams %)	Days before 1st treatment	R.B.C. (millions per c.mm.)	Hgb. (grams %)	Hæmatocrit (%)	Red cell diameter (microns)	Serum iron (gamma %)	U.I.B.C. (gamma %)	Days after 1st treatment	R.B.C. (millions per c.mm.)	Hgb. (grams %)	Hæmatocrit (%)	Red cell diameter (microns)	Serum iron (gamma %)	U.I.B.C. (gamma %)										
1	2920	3.5	8.4	13	3.6	8.4	1	3.3	8.7	34	7.3	10	480	1.5	1.5	24	4.0	12.4	7.6	114	250	270	4.4	12.4	43	7.6	41	315
2	12	3.8	8.6	4	3.6	8.7	1	3.9	8.7	33	7.2			1.25	1.25	95	4.8	14.0	48	7.7		213	4.0	12.2	40	7.7	88	200
3	1161	3.9	9.3	11	3.5	7.8	1	3.3	7.8	28	7.2	10	575	2.5	2.5	23	4.9	13.7	7.7	129	275	174	4.8	14.0	46	7.5	80	370
4				8	4.3	8.1	1	4.2	7.8	30	7.1	8	475	1.8	1.75	49	5.0	14.0	50	7.6								
5	18	3.8	7.8	16	3.7	7.1	1	3.6	7.5	30	7.3	13		2.1	2.1	32	4.7	12.4	47	7.7	125	138	4.3	12.8	43	7.5	121	
6	1286		11.6	8	4.1	11.2	1	3.9	11.0	37	7.2	90	150	1.1	1.1	73	4.3	12.4	40	7.5		102	4.1	12.2	40	7.6	118	115

*Determined by the method of Barkan and Walker (5).
 †U.I.B.C.—Unsaturated iron binding capacity of serum estimated by the method of Cartwright and Wintrobe.⁴

Wilkinson.⁴ There was no difference in tolerance or response to the three preparations.

The total dose was calculated on the basis of 37 mgm. of iron for each 1% deficit of hæmoglobin (Haldane). It has been estimated that about two-thirds of this amount is used for synthesis of hæmoglobin and one-third to replenish stores of iron.⁴ A 50 mgm. dose of iron was given on the first day, 100 mgm. on the second and 200 mgm. on the third and subsequent days. Injections were given from an all-glass syringe into an antecubital vein at a rate not exceeding 5 c.c. per minute. These solutions are strongly alkaline and may cause sloughing when injected into the tissues outside a vein. Care was taken to avoid this.

Toxic reactions.—Reactions to the intravenous administration of many iron compounds are alarming. Irritation of the gastro-intestinal tract may give rise to nausea, vomiting and diarrhœa. Depression of the central nervous system may cause coma. Precipitation of iron particles in the blood may lead to multiple pulmonary and systemic emboli with symptoms like those of fat embolism. These reactions may be fatal. The minimum lethal dose for man is not known but single injections of more than 10 to 20 mgm. have usually produced severe reactions.

It is noteworthy that no toxic reactions were encountered following the 52 intravenous injections of 50 to 200 mgm. of iron as saccharated iron oxide given to the six cases described here. On two occasions patients noticed a sense of warmth in the arm during an injection. No local venous thromboses resulted.

Response to treatment.—Response to treatment was good in every case. Symptoms such as tiredness, dyspnœa, palpitation, loss of appetite and dyspepsia were relieved rapidly. Koilonychia was gradually replaced by normal nail formation. Glossitis and angular stomatitis subsided and the one patient with Plummer-Vinson syndrome was completely relieved of dysphagia. Clinical improvement was apparent as soon as 48 hours after starting treatment. Red blood cell counts and hæmoglobin levels rose quickly and have been well maintained for as long as nine months (Table II). The hæmatologic response was often dramatic, with a reticulocyte peak of 10 to 23% after 6 to 10 days (Fig. 1).

COMMENT

The responses to intravenous treatment with the three saccharated iron oxide preparations were equally prompt and satisfactory. No toxic reactions were encountered. Great care is necessary in the preparation of the solution described by Slack and Wilkinson.⁴ Use of such a preparation for treatment implies a responsibility to first test its toxicity in laboratory animals and ensure that the solution is stable and of correct pH. Feojectin and ferri-venin are more convenient because they have been standardized before release and there is no need for preliminary testing in the hospital laboratories.

It is clear that, in the doses used, these solutions of saccharated iron oxide are safe and effective in the treatment of iron deficiency

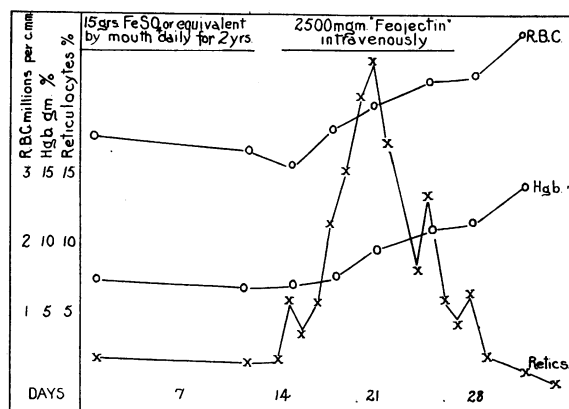


Fig. 1

anæmia. There is no doubt that the development of this agent represents an important advance in therapy. The proper indications for its use cannot be defined at the present time. Most cases of iron deficiency anæmia respond satisfactorily to treatment with iron by mouth and use of the intravenous route is unnecessary. We think that the use of iron by the intravenous route should be restricted to cases of iron deficiency anæmia which cannot be adequately treated with iron by mouth. Saccharated iron oxide is clearly indicated for patients who are refractory to or cannot tolerate iron by mouth, or when replacement of iron is an urgent matter. An example of the last is iron deficiency anæmia late in pregnancy.⁷

The late results of giving large amounts of iron intravenously to patients who have no iron deficit are not known. A condition resembling hæmochromatosis sometimes results from oft repeated blood transfusions. The possibility

that a similar disorder may be produced by the injudicious intravenous use of saccharated iron oxide should be considered.

SUMMARY

1. Six patients with iron deficiency anæmia, refractory to or unable to tolerate iron by mouth, were treated with saccharated iron oxide by the intravenous route.

2. No toxic reactions were encountered although single doses of iron as large as 200 mgm. were used.

3. Response to treatment was good in every case.

4. It is suggested that use of iron by the intravenous route be restricted to cases of iron deficiency which cannot be adequately treated with iron by mouth.

We are grateful to our colleagues of the Departments of Medicine and Surgery of the Montreal General Hospital for their co-operation in the investigation and treatment of these cases.

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SOME EFFECTS OF INTRAVENOUS INJECTIONS OF SACCHARATED IRON OXIDE ON SERUM IRON AND UNSATURATED IRON BINDING CAPACITY*

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TOXIC reactions are seldom encountered when single intravenous doses of iron as large as 200 mgm. daily or twice daily are given as saccharated iron oxide.^{1 to 5} In striking contrast, severe reactions may follow the intravenous injection of small doses of many other iron compounds. It seemed interesting to study the effects of intravenous injections of saccharated iron oxide on serum iron and unsaturated iron

binding capacity (U.I.B.C.) in the hope that this paradox might be resolved.

Holmberg and Laurell,⁶ and Cartwright and Wintrobe⁷ gave single intravenous doses of 1 to 25 mgm. of iron in the form of "ascorbic acid reduced ferric chloride", or "iron ascorbate". Toxic reactions occurred only when the capacity of the serum to bind iron was exceeded. Under these circumstances serum iron levels rose to the limits of the total iron binding capacity, the unsaturated iron binding capacity became zero and the surplus unbound iron rapidly left the blood.

SACCHARATED IRON OXIDE

We used three preparations, each of which contained 2% iron. Two, "feojectin" and "fer-rivenin", were proprietary products.* The third, "M.G.H. 3", was prepared by Mr. F. Zahalan, chief pharmacist of the Hospital, according to the method of Slack and Wilkinson.² There was no difference in tolerance or response to the three preparations.

METHODS

Six patients with iron deficiency anæmia volunteered for these experiments. Single doses of 40 to 200 mgm. of iron as saccharated iron oxide were given from an all-glass syringe into an antecubital vein at a rate not exceeding 100 mgm. per minute. Venous blood was drawn from the opposite arm before the injection, five minutes after the injection, and at various intervals during the subsequent 24 hours. No anticoagulant was used. Serum iron and U.I.B.C. were determined by the methods of Barkan and Walker⁸ and Cartwright and Wintrobe⁷ respectively.

RESULTS

No toxic reactions were encountered. Serum iron and U.I.B.C. values are shown in Table I. Five minutes after each injection the serum iron rose to a level far above the total iron binding capacity of the serum. The U.I.B.C. was reduced but never approached zero. At the end of 24 hours serum iron levels and U.I.B.C. approximated the initial values.

DISCUSSION

It is clear that saccharated iron oxide differs markedly from other iron compounds with respect to toxicity and effect on serum iron and

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