

The Treatment of Iron-Deficiency Anemia with Intravenous Iron Dextran

By SIDNEY MARCHASIN AND RALPH O. WALLERSTEIN

IN THE THERAPY of iron-deficiency anemia, iron given orally is safe, effective, inexpensive, and is usually the treatment of choice, but occasionally when a rapid replenishment of iron stores is desired, administration by the parenteral route is indicated. Heath, Strauss and Castle,¹ in 1938, showed that when 16-32 mg. of iron as ferric ammonium citrate is injected subcutaneously or intramuscularly, practically the total amount is utilized for hemoglobin formation.

Two iron compounds, iron ascorbate² and colloidal ferric hydroxide,³ have been given intravenously in doses of 10 mg., but both proved to be unstable and toxic. The introduction of saccharated iron oxide⁴ and dextriferron (iron dextrin)⁵ about 15 years ago provided improved preparations for intravenous use, for as much as 500 mg. could be injected without causing serious toxic reactions. In 1954, a new compound, iron-dextran complex (Imferon), was found to be effective when given intramuscularly.⁶ Most published accounts have dealt with intramuscular administration of this preparation. In one of the few reports on the intravenous use of iron dextran, Callender and Smith⁷ described toxic reactions in two patients who had been given 50 mg. parenterally, and suggested further study of its administration by the intravenous route. The present investigation deals with the intravenous use of iron-dextran in very large amounts in 45 patients. Most of the injected iron stayed in the blood stream for several hours, was well tolerated and eventually utilized. A preliminary report has been published.⁸

MATERIALS AND METHODS

The subjects consisted of 37 patients with iron-deficiency anemia and eight patients with acute gastrointestinal bleeding. The diagnosis in all cases was supported by the lack of marrow hemosiderin and usually by the characteristic blood picture, low serum iron levels and high total iron-binding capacity. Bone marrow smears were obtained by aspiration; hemosiderin was determined as previously described.⁹ Serum iron was determined by the method of Kok and Wild,¹⁰ slightly modified by using 0.2 N hydrochloric acid as diluent, and by boiling the specimen for 5 minutes before adding trichloroacetic acid. Using this method, 1:10 in vitro dilutions of Imferon in serum gave serum iron concentrations of 5119 $\mu\text{g./ml.}$, which agreed well with the stated Imferon concentration of 50 mg./ml., and with values obtained in our laboratory of 50.40 mg./ml. when undiluted Imferon was first digested for 20 minutes in 2 ml. chloric acid.

From the Hematology Research Laboratory, Children's Hospital, and the Hematology Unit (San Francisco General Hospital), University of California School of Medicine, San Francisco, Calif.

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All patients were given undiluted iron-dextran intravenously. The compound was administered in a single dose of 2000–3000 mg. (6 patients), 1000 mg. (18 patients), 100–500 mg. (7 patients), and in repeated doses of 250–500 mg., 2–4 times in 2 weeks (6 patients). Iron was given by slow intravenous drip infusion to the first few patients; the remainder received the preparation by injection over a 4–10 minute period. One patient (F. C.), who had continued blood loss from congenital telangiectasis, received a second dose of 3000 mg. 2 months after the first injection. Five of the patients had been treated with intramuscularly administered iron-dextran 2–6 months before the intravenous injection. Eight additional patients with severe acute gastrointestinal bleeding received 500–2000 mg. of iron-dextran introduced directly into the transfusion bottle. The patients were carefully observed for untoward local or systemic effects and change in vital signs. Frequent serum iron determinations were made in some cases.

The concentration of iron in the urine was determined after the administration of iron-dextran in 3 patients.

RESULTS

No untoward local reactions were observed. Accidental perivascular infiltration in one patient caused only minor, transient discomfort. One patient developed a delayed systemic reaction, characterized by shaking chills and mild abdominal cramps, approximately 8 hours after intravenous injection of 1000 mg. of iron-dextran; however, she did not develop fever and had no objective abdominal signs or symptoms; she had a similar reaction when iron-dextran was again given intravenously 1 week later. None of the other patients had any discomfort or change in vital signs.

Serum iron levels usually reached a peak in 10 minutes, then gradually declined from levels as high as 95,000 $\mu\text{g.}$ per 100 ml. to 100 $\mu\text{g.}$ per 100 ml. or less in 2 to 4 weeks (fig. 1). Serum samples with an iron content in excess of 12,000 $\mu\text{g.}$ per 100 ml. appeared brown to the naked eye; concentrations of 6000 $\mu\text{g.}$ per 100 ml. did not discolor the serum.

Most of the injected iron could be accounted for in the plasma (table 1). For example, in patient F. C., the pretreatment serum iron level was 29 $\mu\text{g.}/100$ ml. Immediately after administration of 3000 mg. of iron-dextran, the serum iron level rose to 86,750 $\mu\text{g.}/100$ ml.; at 10 minutes it was 95,000 $\mu\text{g.}/100$ ml., at 1 hour 91,000 $\mu\text{g.}/100$ ml., and at 24 hours 78,500 $\mu\text{g.}$ During the first week, the plasma levels decreased in linear fashion at a rate of 525.6 $\mu\text{g.}/$ hour. At 5 weeks, the serum iron level had fallen to 40 $\mu\text{g.}/100$ ml. Only 41 $\mu\text{g.}$ were excreted in the urine during the first 24 hours. In 2 other patients urinary excretion of iron was less than 100 $\mu\text{g.}$ per day for 72 hours. Stainable iron examined in one patient was present in the bone marrow at 12 hours but not at 6 hours.

DISCUSSION

Toxic reactions to intravenously administered iron occur when ionized iron exceeds plasma iron-binding capacity. Normally transferrin, the iron-binding beta-2 globulin, can chelate 8 to 10 mg. of iron. Modern iron preparations for parenteral use owe their lack of toxicity to the complexing of iron with a large, relatively stable colloidal molecule. Iron-dextran¹¹ is a combination of colloidal ferric hydroxide with dextran of a molecular weight of approximately

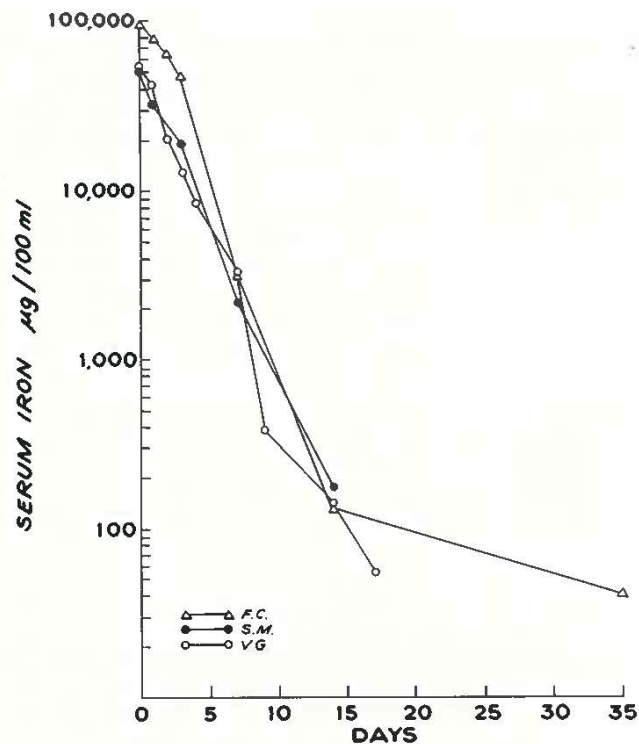


Fig. 1.—Disappearance rate of serum iron after intravenous administration of iron-dextran.

2000 to 8000. The solution contains 5 per cent iron and has a pH of 6. The complex is a weakly negatively charged molecule, whose stability, in contrast to saccharated iron oxide, does not depend on an adsorbed layer of strongly charged ions. Clinically, the stability of iron dextran is demonstrated by the lack of untoward symptoms even when plasma iron levels are extremely high. Despite these levels, iron is not lost in urine and stool in significant amounts, and appears in the marrow only after 6–12 hours. Early plasma levels can account for practically all the injected iron (table 1); it probably is removed slowly by the reticuloendothelial cells.

The indications for the intravenous use of iron-dextran are similar to those for the intramuscular route. Parenteral iron may be given to patients who are (1) unwilling to take iron by the oral route, (2) unable to tolerate it well (e.g., patients with peptic ulcer, regional ileitis or ulcerative colitis), (3) unable to absorb iron well (e.g., in sprue), and (4) to patients who lose relatively large amounts of blood from gastrointestinal lesions that are not amenable to surgical treatment (e.g., congenital telangiectasia, inoperable cancer and blood loss of obscure origin). Occasionally, parenteral iron may be used in patients who fail to respond to oral administration; in these individ-

Table 1.—Serum Iron Levels after Intravenous Administration of Iron-Dextran

	Patient				
	F. C.	S. M.	R. M.	E. C.	V. G.
Weight in Kg.	57.3	53	54	50	57
Estimated plasma volume in ml.	2,865	2,650	2,700	2,500	2,850
Mg. of iron administered	3,000	1,500	1,000	2,000	2,000
Predicted peak in μ g.	104,700	56,600	37,050	80,000	70,200
Actual peak in μ g.	86,750	48,900	24,250	81,000	54,000
Per cent of peak value	62.4	87	78	101	77

uals it is imperative to make a thorough re-evaluation of the diagnosis before proceeding with parenteral therapy. The intravenous route has some advantage over intramuscular injection in (1) bedridden, immobilized patients who have greatly reduced lymph flow and decreased absorption of iron-dextran from the muscle depot, (2) asthenic patients without much muscle mass, (3) patients requiring multiple, relatively large injections of iron who find that intramuscular administration causes discomfort, and (4) patients with severe blood loss from idiopathic thrombocytopenic purpura who may have tissue bleeding after intramuscular injections.

SUMMARY

Iron-dextran, in doses up to 3000 mg., was administered intravenously by single injection to 37 patients with iron deficiency and to 8 additional patients with acute gastrointestinal bleeding. No serious untoward effects were observed. One patient developed chills and mild abdominal cramps 8 hours after injection. Most of the iron could be accounted for in the circulating blood immediately after the injection. Iron was cleared from the plasma slowly for 3 weeks after the administration. Iron-dextran appears to be a safe and well-tolerated intravenous preparation. It is especially useful in the treatment of iron-deficiency in immobilized patients and individuals with small muscle mass.

SUMMARIO IN INTERLINGUA

Dextrano a ferro, in doses de usque a 3.000 mg, esseva administrate per via intravenose in injectiones unic a 37 patientes con carentia de ferro e a 8 patientes additional con acute sanguination gastrointestinal. Nulle serie effectos adverse esseva observate. Un del patientes disveloppava alior e leve grados de crampas abdominal 8 horas post le injection. Le plus grande parte del ferro poteva esser retraciate in le circulation de sanguine immediate post le injection. Ferro esseva catabolisate ex le plasma lentamente durante 3 septimanas post le administration. Dextrano a ferro pare esser un salve e ben-tolerate preparato intravenose. Illo es particularmente utile in le tractamento de carentia de ferro in immobilisate patientes e subjectos con minime massas muscular.

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Sidney Marchasin, M.D., U.S.P.H.S. Hematology Trainee, Hematology Research Laboratory, Children's Hospital, and the Hematology Unit (San Francisco General Hospital), University of California, School of Medicine, San Francisco, Calif.

Ralph O. Wallerstein, M.D., Hematology Research Laboratory, Children's Hospital, the Hematology Unit (San Francisco General Hospital), Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco, Calif.