CLINICAL PROFILES

Intravenous Iron-Dextran Complex

By RALPH O. WALLERSTEIN

WHEN IRON-DEXTRAN COMPLEX became available in 1952 it was widely hailed as an effective, practical, and safe therapy for iron deficiency in children. Iron could be administered in adequate doses without regard to the patient's or mother's ability or willingness to complete a course of oral therapy. The total dose could be given in one to four intramuscular injections. The incidence of untoward reactions was very low, in the neighborhood of 1 per cent; reactions included fever for 1 to 3 days, arthralgia, and regional lymphadenopathy. Early application of the drug to this treatment of iron deficiency anemia during pregnancy was equally successful. However, in adults the larger dosage requirement, the consequent local discomfort and skin stains, and the limitation of volume of the individual dose led to initiation of trials of intravenous administration of the drug.

PHARMACOLOGY

Iron-dextran complex is a stable preparation containing iron complexed with a special fraction of dextran, molecular weight 5,000 to 10,000. This low molecular weight dextran appears to act as a protective lyophilic colloid. The complex contains the equivalent of 5 mg. iron/ml., has a pH of 6.5, and is isotonic with tissue fluids and is stable in the presence of blood; it has a weak negative charge and moves to the anode on electrophoresis. In mice the complex has very low toxicity: The LD_{50} is over 1,000 mg. iron/Kg. of body weight. In determining the chronic toxicity of the preparation, mice, rats, and guinea pigs have been given total doses of as much as 30 times the equivalent clinical dose and, more than a year later, have shown no ill effects whatsoever.[1]

Large doses of iron-dextran complex color human serum brown. This may cause false high readings of serum bilirubin, and low serum calcium, but does not interfere with the performance nor alter the results of other standard laboratory determinations,[2] including typing and crossmatching.[3]

From Hematology Research Laboratory, Children's Hospital and Adult Medical Center, and The Medical Service, San Francisco General Hospital, University of California School of Medicine.

First submitted February 8, 1968; accepted for publication April 24, 1968.

RALPH O. WALLERSTEIN, M.D.: *Associate Clinical Professor of Medicine, University of California.*

Iron-dextran complex is not excreted from the body; only traces can be found in gastric juice, stool, urine,[4] and breast milk,[5] even when the concentration is high in serum. The complex is removed slowly from the blood and is taken up by the liver cells and the reticuloendothelial tissues, from which iron is made available for hemoglobin formation.[6] The half-time disappearance of radioactivity in plasma is 2.5–3 days. Surface scintillation counting shows a progressive increase in radioactivity over the liver, spleen, and sacrum up to the seventh day, followed by a gradual decrease during the next 14 days, so that by the twenty-first day the radioactivity over these sites had fallen to less than the initial value.[7,8] Viewed by the electron microscope, iron-dextran complex is composed of aggregates of closely packed spherical particles, presumably ferric hydroxide aggregates, measuring 1–3 micra in diameter. The same material can be seen in reticuloendothelial cells soon after injection. Ferritin develops in close proximity to the ingestion vacuoles, and it can be identified by its characteristic tetrahedron shape and uniform size. It is apparently synthesized from the ferric hydroxide aggregates. Routine histochemical technics cannot distinguish between these two forms of iron.[7]

Infants of mothers treated with iron-dextran complex late in pregnancy are hematologically normal and do not have excessive amounts of iron in the marrow. Studies on iron in maternal and fetal tissues of pregnant rhesus monkeys treated with iron-dextran complex show that a small portion, up to 4 1/2 per cent, is transferred across the placenta to the fetus; most of the iron is stored in the maternal liver and later appears in circulating maternal red cells.[8]

Indications

Parenteral iron does not raise levels of hemoglobin faster than oral iron; its advantages over tradional therapy are largely technical. It is indicated for the treatment of iron deficiency in the following situations: 1) when administration of iron-dextran complex can replace or avoid transfusions; 2) when patients cannot be relied upon to take iron medication orally as is often the case in a clinic population; 3) when iron absorption is impaired, as in patients with malabsorption syndromes and after gastrectomy; 4) when the oral form of iron is not well tolerated, as in patients with active peptic ulcer, regional ileitis or ulcerative colitis, and in patients with nausea, abdominal distress or change of bowel habits after ingestion of the drug. Intolerance to oral iron may accompany concurrent use of certain drugs that are themselves gastrointestinal irritants, such as chemotherapeutic agents; and 5) when anemia is believed to have more than one cause, and it is helpful to repair the iron deficiency before further investigation is undertaken.

Intravenous administration of iron-dextran complex has several special advantages. A full therapeutic dose can be given in a single injection. The drug is more easily tolerated in individuals who require repeated injections for maintenance of iron balance, as in patients with chronic gastrointestinal blood loss which cannot be repaired surgically, with congenital telangiectasia, with bleeding gastrointestinal malignancies, and in some patients with hiatus her-

nias, or with bleeding sites not detectable even after repeated radiologic examination. It is better absorbed from the injection site in immobilized patients than is the intramuscular injection. Finally, it is particularly useful in patients with bleeding tendencies, such as idiopathic thrombocytopenia purpura, because intramuscular injections can cause hematomas, and intravenously administered iron does not.

Methods of Administration

In general, two methods of administration have been employed. We prefer to give iron-dextran complex undiluted. The total dose is given in a single syringe. Therapy is initiated by first giving 1/2 ml. The needle is left in the vein with a 2 minute wait for possible sensitivity reactions, then an additional 4 1/2 ml. are given over the next 3 minutes. Injections of 10 ml. are repeated at convenient intervals, daily or weekly, allowing 5 minutes per injection. We have not encountered intolerance to repeated intravenous injections, or a problem with alternation of intramuscular and intravenous injections, or with concomitant oral and intravenous administration of iron. This method of intravenous administration is especially useful in treating patients who have chronic blood loss and need some form of maintenance iron therapy, or who are ambulatory and prefer repeated injections to a single infusion requiring hospitalization.

The other method is infusion of the total dose, which is often preferred during pregnancy. It has also been used in cases of hookworm infestation and other field situations where more than one doctor-patient contact was unlikely. The indicated vehicle for infusion of iron-dextran complex is saline in a 5 per cent vol./vol. solution. Initially it is infused at a rate of 20 drops/minute; if no untoward effects occur the rate is increased after a few minutes to 40–60 drops/minute.

Other vehicles for iron-dextran are 5 per cent glucose in water or transfused blood. Dosages usually vary from 500–3000 mg. of elemental iron. Both methods of administering iron-dextran complex intravenously have been uniformly effective in raising the level of hemoglobin rapidly, usually at the rate of 2.5–7.5 Gm./100 ml. in 3 weeks. The amount of iron in 5 ml. iron dextran is equivalent to that in 1 pint of blood or 250 mg. In a 70 Kg. man this represents 10 per cent of the blood volume or 1.5 Gm. of Hb per 100 ml. In a patient of average size we administer about 250 mg. of iron for each gram that the patient's hemoglobin concentration is below normal. This slight excess assures adequate replacement of stores. The table of dosage supplied by the manufacturer may also be followed.

When patients lose blood chronically, it is better to determine the actual amounts lost by labeling the red cells with radioiron or radiochromium. One also can attempt to replace with parenteral iron according to levels of hemoglobin, but many patients cannot reach normal levels, even though they receive large amounts of parenteral iron, because their rate of blood loss exceeds that at which iron is mobilized for hemoglobin formation; excessive amounts of iron could accumulate in the tissues despite chronic anemia. The serum

Table 1.—*Reactions to Intravenous Iron Dextran*

Author	Number of Cases Treated	Number of Generalized* Reactions
4. Marchasin et al.	37	1
9. Gartlan	55	1
10. Varde	307	1
11. Basu	30	0
12. Clay et al.	150	7
13. Dawson et al.	133	5
14. Lane et al.	200	1
15. Smith	18	0
16. Yoffa	16	0
17. Bhatt et al.	75	3
18. Bonnar et al.	500	5
19. Hamstra et al.	225	5
20. Stohlman	15	1
21. Thaman et al.	106	1
6. Will et al.	10	0
22. Malcolm	12	0
23. Manson	101	2
24. Maschas et al.	47	1
25. Pathak et al.	200	0
26. Patel et al.	45	0
27. Newcombe	35	0
28. Ashby	79	0
Total	2396	34

*Does not include fever, lymphadenopathy, arthralgia.

iron and total iron binding capacity should be checked to verify that iron deficiency continues. One must wait for 3 weeks after the latest injection of iron to obtain meaningful serum levels. Examination of the marrow for hemosiderin is less useful because some iron dextran usually remains fixed in the reticuloendothelial cells after parenteral iron therapy.

Untoward Effects

To date over 2,400 patients treated with intravenous iron dextran have been reported in the world literature (Table 1[4,6,9-28]). The incidence of untoward effects has been as low as that associated with the intramuscular route, about 1–2 per cent. Most of the reactions appeared immediately, usually during administration of a test dose. Symptoms reported include flushing, headache, apprehension, dyspnea, cough, pain in the chest, back, or abdomen, lacrimation, photophobia, nausea, vomiting, and bronchospasm. Other manifestations may be hypotension, cyanosis, edema, erythema urticaria, delayed (1 day) arthralgia, lymphadenopathy, and local phlebitis. Iron-dextran therapy occasionally has unmasked latent folic acid deficiency.[11] Phlebitis seems to be more common when the material is diluted and given by intravenous drip, especially when used with 5 per cent dextrose in water, than when the undiluted drug is administered.

Despite this formidable catalogue of symptoms, most of the reactions are

mild and transient and include only a few of those listed; no fatalities have been reported. The method of administration or the type of patient treated has had no consistent relation to the type and the frequency of reactions. All observers agree that the material must not be administered too rapidly: A rate of 50–100 mg./minute should not be exceeded. When reactions did occur in pregnant women no special problems were encountered; i.e., labor was not precipitated and the fetus did not appear to be harmed. Iron overload has not been a problem.

Summary

Experience by many observers in the last few years has shown that intravenously administered iron dextran is a useful and safe agent in the management of iron-deficiency anemia. The conscientious physician, who has diagnosed iron deficiency by the absence of hemosiderin in marrow or by the characteristic serum values for iron and total iron-binding capacity, may well prefer to inject the calculated correct amount of iron rather than depend on the capriciousness of the patient's gastrointestinal tract or pill-taking habits. In clinical situations in which the doctor-patient contacts are severely limited in number, intravenous injection may be the only reliable way to administer the proper amount of iron. Treatment by intravenous injection, only after employing firm diagnostic criteria, may restore iron to its proper place in the physician's armamentarium and elevate it from buckshot to bullet.

SUMMARIO IN INTERLINGUA

Le experientia de numerose observatores in le curso del passate annos ha demonstrate que le administration intravenose de dextrano a ferro es un utile e salve mesura in le therapeutica de anemia a carentia de ferro. Le conscientiose medico, qui ha diagnosticate carentia de ferro a base del absentia de hemosiderina in le medulla o a base del characteristic valores seral pro ferro e pro le total capacitate ferro-ligatori, va possibilemente preferer injicer le correcte calculate quantitate de ferro a fiderse del capriciositate del vias gastrointestinal del patiente o de su habitudes in ingerer pillulas. In situationes clinic in que le contactos de medico e patiente es fortemente restringite in lor numeros, le injection intravenose representa possibilemente le sol fidedigne maniera de administrar le appropriate quantitate de ferro. Le tractamento per injection intravenose—semper, il va sin dicer, post le application de stricte criterios diagnostic—ha le potientalitate de restaurar ferro a su juste rolo in le armamentario del medico e de transformar su application ex un bombardamento indiscriminate ad in un attacco strategicamente precise.

REFERENCES

1. Martin, L. E., Bates, C. M., Beresford, C. R., Donaldson, J. D., McDonald, S. F., Dunlop, D., Sheard, P., London, E. and Twigg, G. D.: The pharmacology of an iron-dextran intramuscular heamatinic. Brit. J. Pharmacol. 10:375–82, 1955.
2. Brown, J., Sahud, M. and Wallerstein, R. O.: Unpublished data.
3. Cox, J. S. G. and Moss, G. F.: Iron-dextran and blood grouping. Brit. Med. J. I:1299, 1966.
4. Marchasin, S. and Wallerstein, R. O.: The treatment of iron-deficiency anemia with intravenous iron dextran. Blood 23: 354–358, 1964.
5. Wallerstein, R. O.: Unpublished data.
6. Richter, G. W.: The cellular transformation of injected colloid iron complexes into ferritin and hemosiderin in experimental animals. J. Exp. Med. 109:197–216, 1959.
7. Will, G. and Groden, B. M.: The treat-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.