The Adverse Effect of Intravenous Iron-Dextran in Rheumatoid Arthritis

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The use of intravenous iron-dextran caused a significant exacerbation of rheumatoid arthritis in 5 out of 7 patients.

DISTURBED IRON METABOLISM has been implicated[1] in the genesis of the anemias associated with rheumatoid arthritis. Clinicians have recommended parenteral iron in the treatment of anemias associated with rheumatoid arthritis even though iron deficiency is not documented by examination of bone marrow stores.[2] During an evaluation of the effect of intravenous iron-dextran* on patients with severe anemia and rheumatoid arthritis, it was noted that intravenous iron-dextran produced an acute exacerbation of the arthritis. This effect has not been found in our search of the literature, nor was it known explicitly to the manufacturers of iron-dextran, though fever and transient arthralgias have been listed as occasional side effects. An extensive review of the use of intravenous iron-dextran in 2400 cases does not mention the exacerbation of arthritis as a side effect.[3]

Patients with typical rheumatoid arthritis who had hemoglobin levels of less than 10.5 Gm. were referred for hematologic evaluation. Table 1 illustrates some of the clinical features of the patients. All were women, and only C.S was hospitalized awaiting remedial joint surgery. None of the patients had subcutaneous nodules. Tests for the presence of LE cells were negative, and liver function tests were normal. Patients C.S., R.B., and E.C. were receiving 5, 10, and 5 mg. of prednisone daily. A complete hematologic evaluation, including a bone marrow aspiration for evaluation of iron stores, was done on each patient. Patients in whom the anemia was thought to be related to the arthritis were subsequently given 1 Gm. of iron-dextran diluted in 500 ml. normal saline intravenously over a period of 1 hour.

A summary of the untoward effects after this treatment of 7 patients by intravenous iron-dextran is given in Table 2. Two types of reaction noted were a febrile response and an exacerbation of the arthritis. Fever was induced only in patients treated at the higher dosage levels of 1.0–3.0 Gm. The fever was as high as 103°F and persisted for 7 days. The flare in arthritis was seen at all dosage ranges used from 0.2–3.0 Gm. In each instance the flare took place only in those joints already afflicted with arthritis. The joints demonstrated increased swelling, heat, and pain. Consultant rheumatologists felt that the ex-

*Imferon, Lakeside Laboratories.

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Table 1.—Clinical Characteristics of Patients Before Iron-Dextran Treatment

Patient	Age	Length of illness, yr.	Latex agglut.	Joints involved
C.S.	48	8	0	Hands, wrists, elbows, shoulders, knees (synovial biopsy in past compatible with rheumatoid arthritis)
A.D.	60	1	0	Shoulders, knees, hands, ankles
R.B.	41	10	1:2560	Ankles, hands
E.C.	50	3	1:640	Hands, wrists, ankles, knees, elbows
R.G.	37	3	0	Hands, knees
M.K.	68	10	1:1280	Knees

Table 2.—Results of Intravenous Iron-Dextran Therapy on Rheumatoid Arthritis

Patient	Bone marrow iron stores	Iron-dextran, Gm.	Exacerbation of arthritis	Duration
C.S.	+	1	+ (fever > 100°F)	1 week
A.D.	+	1 × 3 days	+ (fever > 100°F)	10 days
R.B.	0	0.5	+	3 days
E.C.	0	0.5	+	1 week
	(2 weeks later)	0.2	+	2 weeks
R.G.	0	1.0	No ill effects	
M.K.*	+	0.2	No ill effects	
M.P.†	0	2.6	No ill effects	

* Not anemic.

† No rheumatoid arthritis, but severe iron deficiency secondary to gastrointestinal blood loss.

acerbation was greater than that usually seen in the natural course of the disease. Eosinophilia was absent in peripheral blood and analysis of synovial fluid was not done. In one instance, patient E.C., the second flare-up occurred within 3 hours after the iron-dextran. The other exacerbations took place within 24 hours of the last dose of iron-dextran. Three patients required an increase in maintenance corticosteroids to control the acute symptoms. The exacerbation lasted as long as 2 weeks. Only E.C. had had prior therapy with parenteral iron-dextran.

Case History

The case history of a patient with a severe reaction to iron-dextran is presented in greater detail.

C.S. was a 48-year-old Negro seamstress with an 8 year history of rheumatoid arthritis. The severely affected joints included hands, wrists, elbows, shoulders, and left knee. She had contracture deformities of the elbow joints and marked swelling of the left knee. She had been on prednisone for 2 years and had had several episodes of hemorrhage from peptic ulcer disease. Review of systems was nonrevealing. Physical examination was normal except for pain and swelling in both proximal interphalangeal and metacarpal joints, in both elbow joints, and in the left knee. Flexion contractures were prominent at both elbow joints. Hemoglobin was 10.3 and hematocrit 35. White count was normal. Blood urea nitrogen, fasting glucose, electrolytes, calcium, alkaline phosphatase, SGOT, bilirubin, LE cell preparations, and uric acid were all within normal limits. Serum protein electrophoresis, stools for occult blood, and urinalysis were within normal limits or negative. Latex agglutination test for rheumatoid factor was negative. A synovial biopsy of her knee joint in the past had been interpreted as compatible with rheumatoid arthritis. The patient was given 1 Gm. of iron-dextran intravenously in 500 ml. of normal saline. Within 24 hours, her temperature rose to 102°F, and there was increased heat, tenderness, erythema, and pain over wrists, fingers, shoulders, knees, and ankles. Blood, urine, and throat cultures were obtained and subsequently reported as negative, and chest roentgenogram was normal. She was treated with 50 mg. of hydrocortisone

intramuscularly for 2 days with subsidence of fever and joint discomfort over the next 6 days. The corticosteroids were gradually lowered to 5 mg. of prednisone daily.

The specificity of the reaction to *intravenous* iron-dextran is suggested by the observation that 2 of the patients (R.B. and E.C.) received the same dosage *intramuscularly* several weeks later with no ill effect. The possibility of a contamination in the medication causing the reaction directly, or causing the iron to dissociate from the dextran, appears to be excluded because two patients (R.B. and M.K.) received treatment from the same batch of medication without ill effect. Patient M.P. (without rheumatoid arthritis) actually received a "total dose infusion" to compensate for iron-deficiency related to gastrointestinal blood loss and had no untoward reaction.

Discussion

It became apparent that the intravenous use of iron-dextran, even in small doses, was accompanied by a risk of a flare in the rheumatoid arthritis. The severity of the reactions precluded any attempts to conduct additional studies on the mechanism of the reaction. Much experience with intramuscular iron-dextran in rheumatoid arthritis without ill effects has been described in the iterature, and such adverse effects have not been associated with the use of this drug by our referring rheumatologists.

It has bee appreciated that there can be an associated arthritis in hemachromatosis.

A relationship of the arthritis to the deposition of iron in the synovial tissues[4] is a reasonable presumption. In rheumatoid arthritis, the amount of iron in synovial tissue greatly exceeds that seen in osteoarthritis or normal tissue.[5] There is evidence that iron-dextran per se may induce joint inflammation: for example, injection of iron-dextran into a knee joint of a rabbit will produce joint inflammation.[6] A possible explanation for our findings is that intravenous iron-dextran is followed by an acute rise in the serum level and, in turn, by an increased concentration of iron-dextran in the synovium and/or joint fluid.

The older literature does not record ill effects of intravenous iron saccharate, but it should be noted that this was given in 200 mg. doses daily over a period of 1 month. Iron-dextran in this study was given over a 1 hour period. Perhaps this material results in local relief of lysosomal material, resulting in an increase in the severity of inflammation. Iron saccharate administration is accompanied by a much higher incidence of immediate side effects since it is not as stable a complex as iron-dextran. The possibility remains that the dextran component of iron-dextran is the provocative agent. This was not tested directly, as the physicochemical structure of the dextran complexed with iron is significantly different from that dextran which is not complexed with iron.* The molecular weight of the dextran in iron-dextran is 5000 to 10,000, and since infusion of low molecular weight dextran has been associated with anuria[9] we did not elect to study its effect. It appears toid arthritis with this compound intravenously.

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*Personal communication from Dr. W. C. Janssen.

Summario in Interlingua

Le uso intravenose de ferro e dextrano causava un exacerbation significative de arthritis rheumatoide in cinque de septe patientes.

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