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INTRAVENOUS IRON IN TREATMENT OF HYPOCHROMIC ANAEMIA ASSOCIATED WITH RHEUMATOID ARTHRITIS

BY

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In a previous communication (Sinclair and Duthie, 1949) we reported the results following the administration of intravenous iron in 23 cases of rheumatoid arthritis with hypochromic anaemia. These cases have now been followed up for periods varying from 7 to 23 months. A further 28 cases have been studied in respect of the haemoglobin response and changes in the erythrocyte sedimentation rate (E.S.R.) following 1 g. of intravenous iron. Iron absorption has been measured in seven cases. In four cases large doses of ascorbic acid have been given in order to assess its effect on the utilization of iron.

Haemoglobin percentages were estimated by a photo-electric colorimeter graduated to register 14.8 g. Hb per 100 ml. as 100%. Westergren tubes were used to measure the E.S.R. Wintrobe's dry mixture of ammonium and potassium oxalate served as an anticoagulant. No correction for anaemia was made, as no reliable method is available. Davis (1946) states that correction for anaemia is usually unnecessary if the Westergren method is used, and that such correction may lead to fallacious results. The moderate degree of anaemia present in most cases of rheumatoid arthritis would be unlikely to influence the E.S.R. to any significant extent.

Results

Follow-up of First Series.—Of the original 23 cases 16 responded to intravenous iron ("ferrivenin"), and seven remained refractory. Of the 16 cases that showed a satisfactory rise in haemoglobin percentage 13 have maintained this level without further iron for periods varying from 7 to 23 months. In the remaining three cases the initial response was not maintained; but all three responded to a second course. Details are given in Table I. Of the seven refractory cases, three received a second course without effect.

Results in Second Series.—Twenty-eight new cases have been given courses of intravenous iron. All were subjected to the same basic regime as the original cases and showed no significant response to oral iron for one month. In 14 cases the preparation used was ferrivenin. A test dose of

TABLE I.—Follow-up of 16 Cases with Good Haemoglobin Response to Intravenous Iron

Case No.	Haemoglobin %			
	After 1 Month on Iron by Mouth	Response to Ferrivenin 1.05 g. Intravenously		
		1 Month After Injection	Final Level	Time in Months
1	79	83	96	13
2*	66	87	90	13
3	72	92	92	9
4	68	80	100	23
5	71	90	90	11
6	74	96	96	14
7*		65	84	12
8	76	88	96	17
9	65	78	82	9
10	70	82	93	7
11*	63	83	93	10
12		76	86	13
13	82	97	96	9
14	75	90	96	16
15		75	84	7
16	80	92	100	15

* Required second course.

50 mg. was followed by 200 mg. daily for five days. In the remaining 14 cases "iviron" was used. A test dose of 200 mg. was followed by 400 mg. daily for two days. Mild toxic symptoms were encountered occasionally with both preparations. These have become very much less frequent since all-glass syringes were adopted in place of glass and metal syringes. In 22 cases a good haematological response was obtained. The average haemoglobin percentage in these cases on admission to hospital was 70. After one month on oral iron it was 71.8. One month after 1 g. of intravenous iron the average figure was 84.3. At three months the average figure was 87.1. In the remaining six cases in this group the response was poor or absent.

Iron Absorption.—To ascertain whether faulty absorption of iron from the gut might explain the failure of these patients to respond to iron by mouth, serum iron values were measured after the administration of 18 gr. (1.2 g.) of ferrous sulphate in seven cases. The method used was that described by Dahl (1948). The results are shown in Table II. In all seven cases serum iron values and absorp-

TABLE II.—Serum Iron Absorption (7 Cases)

Time	Serum Iron Levels μ g. per 100 ml.						
10 a.m. (before oral iron) ..	90*	83	66	89	90	75	94
12 noon (after 18 gr. oral iron)	200	126	—	166	150	83	146
2 p.m. " " " "	210	250	200	116	150	110	155
4 p.m. " " " "	160	83	56	106	80	96	103

* In spite of good absorption curve there was no appreciable rise in haemoglobin level following two courses of intravenous iron.

tion curves fell within the normal range. In six cases the response following the administration of 1 g. of iron intravenously was satisfactory. In one case no rise in the haemoglobin level followed the administration of a total of 2 g.

Erythrocyte Sedimentation Rate.—A fall in E.S.R. was noted in cases responding to intravenous iron in the first series of cases studied. This point has now been investigated in more detail. In 10 cases the E.S.R. was measured daily during the course of injections. The results are given in Table III. It will be noted that in six cases showing a good response the E.S.R. fell sharply, while in the four refractory cases there was no significant alteration in rate. Five cases were selected in which haemoglobin values were 80% or over but in which the E.S.R. was markedly raised. After 1 g. of intravenous iron the rate fell and the haemoglobin percentage rose in all five (Table IV). In Case 5 the

TABLE III.—The E.S.R. in 10 Cases Responding to Intravenous Iron

Case No.	E.S.R. (mm. in 1 Hour)				Initial Hb%	Final			Re-sponse
	Before 1st Injection	Before 2nd Injection	Before 3rd Injection	1st Day After 3rd Injection		Hb%	E.S.R.	Time in Days	
1	100	39	29	60	57	99	25	50	Good
2	37	21	4	25	78	90	12	19	"
3	73	38	65	64	60	84	48	30	"
4	35	33	17	24	79	96	40	67	"
5	100	100	40	—	69	89	62	24	"
6	45	35	34	5	76	91	28	49	"
7	103	102	98	96	66	72	72	59	Poor
8	60	—	96	90	72	79	84	25	"
9	78	69	69	—	72	75	72	15	"
10	95	90	97	115	78	70	110	32	"

TABLE IV

Case No.	E.S.R. (mm. in 1 Hour)			Initial Hb%	Final		
	Before Injection	After Injection	Time in Days		Hb%	E.S.R.	Time in Days
1	90	52	6	87	100	24	102
2	72	40	4	81	96	33	146
3	60	23	11	80	95	42	29
4	70	27	7	81	97	16	90
5	60	48	7	82	97	—	—
5*	90	45	3	78	90	28	133

* Second course.

fall in E.S.R. was only moderate. In five weeks the haemoglobin level fell and the E.S.R. rose again. A second course brought a more marked fall in E.S.R. Haemoglobin percentage rose to 90 and has been maintained at this level.

Effect of Ascorbic Acid.—The plasma ascorbic acid in rheumatoid arthritis is often subnormal (Rhinehart *et al.*, 1937). Tötterman (1949) could find no correlation between plasma ascorbic acid values and the ability of the organism to utilize iron. It was felt, however, that the point was worthy of further investigation. Four patients were given 1 g. of ascorbic acid intravenously on three successive days. There was no significant change in the E.S.R. or haemoglobin percentage. Seven days later the same patients were given 1 g. of ascorbic acid along with each of three injections of iviron (total 1 g.). The fall in E.S.R. and the rise in haemoglobin levels were of the same order as those which followed intravenous iron alone.

Effect of Intercurrent Infection.—A patient whose response to intravenous iron had been good (haemoglobin rose from 80% to 91%) developed a large abscess in the gluteal region. The haemoglobin dropped to 79% in the course of three weeks. The abscess was opened and drained, and the haemoglobin rose to 89% without further iron. The infection recurred, and the haemoglobin again fell to 79%. When healing finally took place the haemoglobin rose to 90% and the E.S.R. dropped from 70 to 20 mm. in one hour.

Subjective Responses.—The majority of patients who eventually show a good response to intravenous iron remark on a feeling of increased well-being and improved appetite immediately after the course of injections, before there has been any change in the haemoglobin level.

Discussion

The response to intravenous iron has now been studied in 51 cases of rheumatoid arthritis with hypochromic anaemia, proved to be resistant to iron by mouth in adequate doses. A satisfactory rise in haemoglobin level was shown in 38 cases; and 13 remained refractory. Of the latter, eight have received a second course, but only two have responded.

Hypochromic anaemia is a common complication of many chronic infections, and in the past has often been

ascribed to a toxic depression of the marrow. It has been presumed that the anaemia in rheumatoid arthritis belongs to this group, though the aetiology of the disease remains obscure. Anaemia due to a toxic depression of the marrow would not be expected to respond to iron given by any route. The fact that a significant number of cases do respond when iron is given intravenously in large doses suggests that the anaemia is due to an increased need of the tissues for iron. This demand apparently cannot be met by the oral administration of iron, even though absorption from the gut is normal. Vannotti and Delachaux (1949) and Tötterman (1949) have both shown that in the presence of infection iron given intravenously is rapidly removed from the blood. It is only since preparations of iron which can be given intravenously in large doses became available that it has been possible to show that haemoglobin levels can be restored to normal in some cases completely resistant to iron given by mouth. It seems reasonable to presume that it is only when the needs of the tissues have been met that an excess of iron becomes available for the formation of haemoglobin in these cases. Iron utilization does not appear to be favourably influenced by the administration of large doses of ascorbic acid.

The striking fall in E.S.R. which has been observed in those cases responding to intravenous iron requires further investigation. No readily acceptable explanation presents itself. An increase in the E.S.R. is closely related to alterations in the pattern of the serum proteins (Ham and Curtis, 1938). Detailed studies of the serum proteins before and after the administration of iron by the intravenous route may shed some light on this problem.

Summary

Intravenous iron was given to 51 cases of hypochromic anaemia associated with rheumatoid arthritis. These cases had all proved resistant to oral iron.

A satisfactory rise in haemoglobin levels was shown in 38 cases.

Thirteen cases remained refractory. Eight of these were given a second course, but only two showed a response.

Twenty-three cases have been followed for periods of 7 to 23 months. Haemoglobin levels have been maintained in 13 of these cases without further iron. Three cases which responded initially required a second course.

Iron absorption was measured in seven cases and was found to be within normal limits.

Cases responding to intravenous iron show a rapid fall in E.S.R.

Ascorbic acid does not materially improve the response to intravenous iron.

It is suggested that in rheumatoid arthritis there is a marked increase in the need of the tissues for iron. Only when this need is met by large doses of iron intravenously does iron become available for the formation of haemoglobin.

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