INTRAVENOUS IMFERON DRIP FOR IRON DEFICIENCY ANAEMIA

by

S. BHAGWANANI,* M.D.

S. SIKAND,** M.D.

and

S. VOHRA***

The obstetrician in India has frequently to take on the responsibility of a patient who, only a few weeks from term, is severely anaemic and grossly deficient in iron. The time is too short to assess the response with oral therapy as the latter depends on the tolerance and on adequate absorption. The gynaecologist is also often faced with a similar problem prior to major surgery.

Intramuscular therapy necessitates hospitalisation or frequent trips to the hospital. Moreover, it causes pain and discolouration and results in abscess formation in 8-9% of cases (Bhatt *et al*, 1966). The fact that the total iron requirement of the patient may be met with in one or two doses is of great value. Nissim, in 1949, administered intravenous infusion of 1,000 mgm. of iron, as saccharated iron oxide, to the patients with practically no reactions. Scott (1954) used saccharated ferrous and ferric oxide in six patients as intravenous infusion without any untoward reactions. Menda (1957) concluded that the infusion was safe after his experience with 30 cases. Iron dextran (Imferon) is a combination of colloidal ferric hydroxide with dextran. Its molecular weight is approximately 180,000 (Lundin, 1961; Davidson *et al*, 1965). The solution contains 5% iron and has pH of 6. Toxic reactions to intravenously administered iron occur when ionized iron exceeds the plasma-binding capacity. Normally transferrin, the iron binding B globulin, can chelate 8-10 mgm. of iron (Marchasin and Wallerstein, 1964). Imferon owes its relative lack of toxicity to its large stable colloidal molecule, freedom from ionic iron and relatively low pH. The stability of iron dextran is demonstrated by the lack of untoward symptoms, even when plasma iron levels are extremely high. Iron is not lost in urine and stool in significant amounts despite these high levels. It appears in the bone marrow only after 6-12 hours. It is probably removed slowly by reticulo-endothelial cells (Marchasin and Wallerstein, 1964). Basu (1963), Lane (1963), Powel (1963), Marchasin and Wallerstein (1964),

*Lecturer.

**Reader.

***Lecturer.

Dept. of Obstetrics & Gynaecology, Lady Hardinge Medical College, New Delhi.

Received for publication on 3-10-1968.

Gartlan (1964) and Bhatt *et al* (1966) have advocated its used as an infusion. Clay *et al* (1965), however, do not feel an infusion justifiable in view of the number of severe reactions even though in the large majority of their cases they had satisfactory response.

Material and Methods

Forty-six cases were chosen from the patients with iron deficiency anaemia admitted to maternity and gynaecological wards of the Lady Hardinge Hospital, New Delhi, from July 1966 to March 1967 for this study. Patients with secondary cardiac involvement, chest infection, specially bronchial asthma and tuberculosis, toxaemia of pregnancy, renal disease and frank sepsis were excluded as reactions are reported to be more common in these cases (Bhatt *et al*, 1966). Later in the series, patients with haemoglobin less than 4 gms.% were also avoided.

Total dose was calculated accordin to the formula 0.3 W (100—Hb% of the patient) as recommended by Bhatt *et al* (1966). W is the weight of the patient in lbs., 100 being equal to 14 gm.%. 500 ml. of 5% glucose or normal saline were used for the infusion; concentrations stronger than 5% v/v were mostly avoided. Two infusions were therefore given on different days, if total dose required was more than 1,500 mgm. An attempt was usually made to give the second infusion within seven days of the first as advised by Powel (1963). Twenty-five mgm. of imferon diluted in 10 c.c. of 5% glucose or saline were given slowly as a test dose, half an hour prior to the first infusion. The drip was started at a rate of 15 drops per minute. The rate was increased to 30-40 drops per minute after half an hour if there was no reaction. The infusion usually was completed between 4-8 hours unless it had been discontinued for some reason. Special care was taken to avoid contamination of the set or the site with alcohol, detergents or strong electrolytes, as these may lead to instability of the iron dextran complex.

Investigations

Haemogram with peripheral smear, urine analysis and repeated stool examinations were done in all cases. Post-infusion haemoglobin estimation was done after 24 hours, 48 hours, 1 week and then every week till six weeks in as many cases as possible.

Observations

The majority of patients were between 20-29 years of age. Two patients were above the age of forty.

Eighteen patients were pregnant, 15 were in the postpartum period and 7 had had abortion and 6 were gynaecological cases.

Table I shows the haemoglobin percentage in these cases at the time of infusion.

TABLE I

Showing haemoglobin percentage in 46 cases

Hb. percentage	3.1-4 gm. %	4.1-5 gm. %	5.1-6 gm. %	6.1-7 gm. %
No. of cases	13	9	16	8

The average time taken for completion of the drip was 6.1 hours. Ten cases had been given one or more units of blood as an emergency. Worm infestation was detected in 12 cases — hookworm in 10 cases and round worm in 2 cases.

Four patients had reactions after the test dose.

Table II shows the average, minimum and maximum rise in haemoglobin in the remaining 42 patients. All the patients had to have repeated haemoglobin estimation at varying intervals after the infusion. Fig. 1 shows the same in a graphic form. Haemoglobin was estimated 24 hours after the infusion in 9 cases and 2 of these showed a rise of 0.5 gm%. Thirteen of the twenty-four cases studied 48 hours after the drip showed a rise of 1-1.5 gm%. In one case, the haemoglobin rise was 2 gm%. Eleven cases with a haemoglobin of 4 gm.% or less were infused. The average rise in these cases during the first week was 2.2 gm.% as compared to 1.25 gm% in the overall group. Delayed response was seen in 3 cases only.

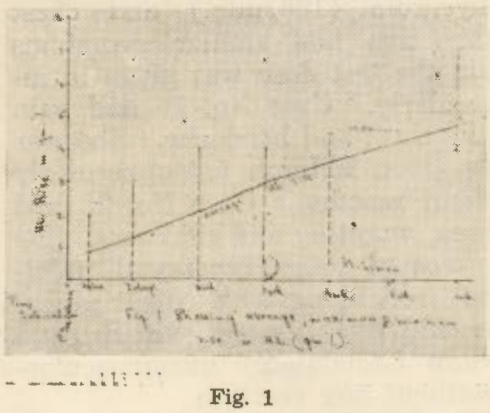

Fig. 1

TABLE II

Showing haemoglobin rise after imferon infusion in 42 cases

No. of cases	Time interval	Average Hb. rise	Maximum Hb. rise	Minimum Hb. rise
9	24 hrs.	Not calculated (Only 2 cases showed rise of .5 gm.).	0.5 gm. %	0
24	48 hrs.	0.85	2	0
35	1 week	1.25	3	—2.5 or 0
29	2 weeks	2.1 (Difference 0.85)	4	0
18	3 weeks	2.9 (Difference 0.8)	4	0.5
10	4 weeks	3.65 (0.75)	4.5	0.5
8	6 weeks	4.75 (Difference in 2 weeks 1.10 gm.)	7	4.0

TABLE III

Showing iron infusion and rise in haemoglobin percentage

Author	No. of cases	Type of infusion	Rise in Hb.
Menda (1957)	30	Single drip infusion with uniferon.	10.18 % in 1st week
Parikh (1957)	15	do.	0.97 % daily rise.
Lane (1964)	53	Imferon infusion	1.03 gm. % per week for 4 weeks.
Bhatt et al (1966)	75	do.	1.0 gm. per week.
Present series	46	do.	1.25 gm. % during first week.

Reactions

Four patients had reaction with the test dose. Case No. 6, 34 weeks pregnant, had a transient fall of blood pressure to 80 mm. Hg. systolic. She improved within half an hour with injection of antihistaminic (Andental) and efcorlin. Case No. 8 had marked dyspnoea and tachycardia (160/min.) and chest pain. She had similar symptoms when the test dose was given intramuscularly. Case No. 16 had pain in the chest and headache. She was later given Imferon intramuscularly without reaction. Case No. 28 had nausea, vomiting and giddiness. She was treated with "Hypercytal" (Colloidal iron along with cobalt gluconate and liver extract, vit B_{12} and Sodium Cacodylate) intramuscularly without any reaction.

Eleven (26%) out of 42 cases had some sort of general reaction including rigor and fever with the first or second infusion (Table IV). The infusion had to be stopped only in 3 cases (7.1%). Two cases had severe rigor and one case (No. 10) collapsed soon after the start of the second drip. She also became unconscious for about three hours and developed hemiplegia. She showed marked improvement within 48 hours and later made a complete recovery.

Discussion

The correct treatment of iron deficiency anaemia would naturally be to supply enough iron to meet the requirements of the bone marrow and depleted iron stores. The fact that the total iron requirements of the patient may be met by one or two treatments is of great importance.

The overall response was good in the present series (Table II) and compares favourably with that obtained by other workers using either saccharated oxide of iron or dextran complex for the infusion (Table III). An increase in haemoglobin, seen as early as 48 hours, is rather unexpected. Bhatt *et al* (1966) also observed a rise of 1-2 gm.% in 30 out of 75 cases within 48 hours. They did not find this rise as entirely beyond explanation, as radioactive iron can be demonstrated in R.B.C. as early as 2 hours.

TABLE IV

Showing reactions with intravenous imferon infusion in 46 patients

No. of patients	No. of patients with reaction to test dose		No. of patients with reaction to infusion	
46	4		11	
	Transient fall of B.P.	1	**Severe**	
	Dyspnoea & tachycardia	1	Collapse with neurological disturbance	1
	nausea, vomiting, giddiness	1	Severe rigors	2
	chest pain and headache	1	**Moderate**	
			Severe muscle pains	6
			Urticaria & giddiness	1
			Fever usually associated with other reactions	7
			Local	
			(Associated with usually some general reaction)	3
			Thrombophlebitis	3
			Lymphadenitis	2

Many workers have reported that the rise in haemoglobin was more rapid in a severely anaemic patient. It would be difficult to comment on this in the present series as none of the patients had an haemoglobin of above 7 gm%. However, the average rise was 2.2 gm.% during the first week in patients with an haemoglobin of 4 gm.% or less as compared to 1.25 gm.% in the overall group. A delayed response has also been noted in some cases by other workers. We encountered three cases in our series. One such case was the patient who collapsed and developed hemiplegia. The fall in her haemoglobin level could be due to the severe reaction she had. In case No. 4, no obvious reason could be found for the delayed response. She was 34 weeks pregnant, 5th gravida and complained of diarrhoea, sore mouth, weakness and oedema of legs and feet. She had fever (100°F) before and after the drip. She had also taken oral iron for a month without any improvement. She had one infusion only. Her haemoglobin was 4.5 gm.% on the day of infusion and 3 gm.%, 3 gm.%, 6 gm%, 6 gm.% and 8 gm.% on 5th, 7th, 11th, 17th and 24th day of the infusion respectively. Case No. 7, however, had hookworm infestation which could account for her lack of response, though initially she showed some improvement. Her haemoglobin rose from 4.5 gm.% to 5.5 gm.% on the 3rd day and 6.5 gm.% on the 7th day. It remained stationary after that for 28 days.

Reactions

The reaction rate of 26% in our series is more than that reported by most of the workers. In a series of 45 cases, Marchasin and Wallerstein (1964) had mild reaction in one case and moderate reaction in another. Lane (1964) reported reactions in 5.6%, one of the patients had a severe anaphylactoid type of reaction.

Gartlan (1964) reported two reactions. One mild and one moderate in 55 infusions. Bhatt *et al* (1966) had severe reactions in 3 out of 75 cases. Clay *et al* (1965), however, did not consider the drip safe in view of the serious reactions in their series. Out of 150 cases, 13 had reactions—6 moderate and 7 severe.

Severe reactions were observed in 3 cases in the present series. One had marked dyspnoea and chest pain after the test dose (Case No. 8). Case No. 10 had had oral and intramuscular iron. The second infusion was given after a lapse of 9 days, more than that advised by Powel, (1963). These factors could account for the reaction in her case. Case No. 46 had severe muscle pain, chest pain and dyspnoea after the infusion. Reactions were moderate in all other cases. It would be difficult to comment whether rigors and fever were due to imferon or due to a pyrogen reaction in spite of all possible aseptic precautions. By far the most striking complaint was severe pain in all the muscles within 24 hours of the infusion. There was marked tenderness in the muscles of both extremities, specially in the calf muscles. All these patients, with one exception, also had intermittent fever ranging from 100-103°F. Fever lasted for 2-5 days. Stiffness of muscles and joints has been re-

ported by Clay *et al* (1965). Marchasin and Wallerstein (1964) reported severe abdominal cramps in one case, 8 hours after the drip. It may be that this type of reaction would decrease if the total dose were calculated to make up haemoglobin up to 12 gms.% and not 14 gm.% as was done in the present series. However, similar types of severe body pains and lymphadenitis have also been observed by us after the use of intramuscular iron. Menon (1965) observed that muscle and joint pains were the commonest reactions after intramuscular iron. Bhatt *et al* (1966) advised adding only 500 mgm of Imferon per 540 c.c. of glucose or saline. Marchasin and Wallerstein (1964), however, hardly had any reactions even with very high concentrations. The concentration of the drp did not seem to have any effect, one way or the other, in the present series, too.

Bhatt *et al* (1966) did not report any reactions in gynaecological patients. Clay *et al* (1964) also did not observe any reactions in postnatal cases. No such distinction was observed in the present study. Neither was any association observed with hookworm infestation.

The reactions were observed to be more frequent in those cases who had had previous iron therapy (oral or parenteral) and pyrexia, even though the patient was afebrile at the time of the infusion.

Local thrombophlebitis was observed in 3 cases (6.5%). Lane *et al* (1964) reported an incidence of 33% but claimed that it had decreased to 5% after the concentration had been reduced to 3-4% V/V.

In view of the occasional serious reactions, imferon infusion should be given with great caution. It should be avoided in cases who have had sepsis or iron therapy in the recent past. Patients with haemoglobin less than 4 gm.% should also be excluded. They are not more prone to reactions but should a severe reaction occur, it would be more dangerous to them.

Summary

The results of imferon infusion have been evaluated in 42 cases of iron deficiency anaemia. Sixty-six infusions were given.

The average rise of haemoglobin was 1.25 gm.%, 0.85 gm.%, 0.8 gm.% and 0.75 gm.% at the end of the 1st, 2nd, 3rd and 4th week respectively.

Four patients had reaction with the intravenous test dose. The reaction rate with infusion in the remaining 42 patients was 26%. Serious reactions were observed in 3 cases (7.1%). Reactions were seen to be more frequent in patients who had had iron therapy or sepsis in the recent past.

Acknowledgement

We are grateful to Dr. (Miss) M. Chaudhuri, F.R.C.S., Principal and Medical Superintendent, Lady Hardinge Medical College and Hospital, New Delhi, for permitting us to use the hospital records. Our thanks are also due to Dr. (Mrs.) P. Madan, F.R.C.O.G., Prof. of Obstetrics and Gynaecology, Lady Hardinge Medical College and Hospital.

References

1. Basu, S. K.: Lancet. **1**: 1430, 1963.
2. Bhatt, R. V., Joshi, S. K. and Shah, M. C.: Am. J. Obst. & Gynec. **94**: 1098, 1966.
3. Clay, B., Rosenberg, B., Sampson, N. and Samuels, S. I. Brit. Med. J. **1**: 29, 1965.
4. Davidson, W. M., Flute, P. T. and Preece, J. M.: Practitioner. **194**: 156, 1965.
5. Gartlan, G. J.: Brit. Med. J. **1**: 435, 1964.
6. Lane, R. S.: Lancet. **1**: 852, 1964.
7. Lundin, P. M.: Brit. J. Cancer. **15**: 838, 1961.
8. Marchasin, S. and Wallerstein, R. O.: Blood. **23**: 354, 1964.
9. Menda, M. K.: J. Obst. & Gynec. India. **7**: 199, 1957.
10. Menon, M. K. K.: J. Obst. & Gynec. India. **15**: 127, 1965.
11. Nissim, J. A.: Lancet. **2**: 49, 1947.
12. Parikh, M. N. and Sequeira, E. S.: J. Obst. & Gynec. India. **9**: 373, 1959.
13. Powel, R.: Lancet. **2**: 252, 1963.
14. Scott, J. M.: J. Obst. & Gynec. Brit. Emp. **61**: 641, 1954.