OBSERVATIONS ON THE USE OF IRON SORBITAL CITRATE IN ANAEMIA IN PREGNANCY

by

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Parenteral iron therapy has been increasingly used since 1947 when Nissin first introduced saccharated oxide of iron for intravenous use. Iron for intramuscular use was first introduced by Anderson and Bergstrom in 1956 as Iron Dextran. Since then a variety of iron preparations have appeared for parenteral use. It is now conceded by most workers that intramuscular iron is a safe and useful therapeutic procedure and its toxicity is much less than that of intravenous iron.

In a clinical trial with Iron Dextran (Imferon) in the treatment of anaemia in pregnancy Menon and Willmott (1960) while reporting satisfactory clinical response to treatment also recorded reactions serious enough to invite attention in 16.9% of cases. One of these patients died. These reactions were mainly encountered in the group of patients with dimorphic anaemia.

Another iron preparation "Jectofer" for intramuscular injection has recently been presented by Lindvall and Anderson (1961). The active substance consists of iron sorbitol citric acid with dextrin as stabiliser. This complex is of low molecular weight, below 5000. It is rapidly absorbed from the site of injection by the blood as well as by the lymph and is rapidly utilised by the bone-marrow. Animal experiments show that in rabbits 2/3rd of the iron is removed in three hours and 80% in 12 hours, there being a sharp rise in the serum iron levels soon after injection. About 30% of the dose of iron is excreted in the urine (Lindvall and Anderson 1961). It is also said to have very little side-effects or toxic reactions and hence it was decided to carry out clinical trials with Jectofer in the treatment of anaemia in pregnancy.

Methods and Materail

Only pregnant women with haemoglobin levels below 7.5 gms.% (estimation by photo-electric colorimeter) were admitted for the trials. In addition to the routine haematological investigations — namely estimation of haemoglobin, red blood cell count determination of packed cell volume, mean corpuscular volume, mean corpuscular haemoglobin concentration, smear examination and bone marrow biopsy — study of the marrow for iron storage, estimation

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of serum proteins by paper electrophoresis, serum iron and total iron binding capacity of serum was done in as many cases as possible at the start and after the treatment. The pattern of iron absorption after an injection of 250 mgms. of iron sorbitol citrate was studied in 4 cases. The haemoglobin and packed cell volume estimations were repeated at weekly intervals until the calculated dose of iron was given. The iron requirements were calculated according to the formula laid down by the manufacturers based on the body weight and haemoglobin percentage. A daily dose of 100 mgms. was given deep intramuscularly in the gluteal region. Those with dimorphic anaemia were given in addtion 15 mgm. of folic acid daily. All patients in the study were admitted into the hospital and looked after by a single medical officer.

Observations and Results

Sixty pregnant women at varying terms of pregnancy with haemoglobin levels below 7.2 gm.% were studied on the above lines. Twenty-four were less than 28 weeks pregnant and in 36 the pregnancy ranged from 28-34 weeks. There were 15 primigravidae, 38 were gravidae 2-5 and 7 were sixth gravidae and over. All patients presented the classical clinical picture of severe anaemia with marked pallor and oedema. In two in addition, marked dyspnoea was also present. The type of anaemia was microcytic hypochromic in 27 and dimorphic (macrocytic hypochromic) in 33. In the latter group the marrow was megaloblastic in 18 and normoblastic in the rest. When stained for iron with potassium ferrocyanide the marrow specimens of all patients showed very markedly deficient storage of iron. Sixteen patients had, in addition, pre-eclamptic toxaemia, blood pressure ranging from 140/90 — 180/110 mm. of Hg. and urine albumin from a trace to 2 +. The distribution of haemoglobin levels in the 60 patients is shown in Table I below.

TABLE I

Hb level in gm%	No. of cases and duration of pregnancy	
	Less than 28 weeks	Above 28 weeks
5 to 7.2	6	11
Less than 5	18	25
Total	24	36

There were 8 patients with haemoglobin levels of 2.5 gm.% or less.

Iron Absorption

The absorption of iron was studied in 4 patients by two hourly estimation of serum iron after an injection of 250 mgms. of iron sorbitol citrate. The estimation of serum iron was repeated at the end of 24 hours, 48 hours and at the end of the course of treatment. Table II below gives the serum iron values in gamma after an injection of 250 mgm. of Jectofer.

These figures demonstrate the rapid absorption of iron from the site of injection. A peak is reached within two hours after which the serum iron levels gradually fall.

In 45 patients the serum iron levels and total iron-binding capacity were estimated prior to and weekly during treatment until it was completed. The average initial serum iron value

before treatment in cases of dimorphic anaemia was higher than in cases of microcytic anaemia. At the end of treatment the serum iron values had reached normal levels. In Table III is shown the range and average serum iron and the total iron-binding capacity of serum values:

Serum Proteins

The serum proteins were estimated by paper electrophoresis in 45 patients. The average values are given in table below and compared with values in non-pregnant and normal pregnant women.

It will be observed that in anaemia in pregnancy there is a marked definite lowering of total proteins and all its fractions.

Response to Treatment

The response to treatment from the clinical point of view was quite satisfactory. In assessing the haematological response stress was laid on the rise in haemoglobin and packed cell volume values. These values were determined every week till the course

TABLE II

	0 hrs	+2 hrs	+4 hrs	+8 hrs	+8 hrs	+24 hrs	+48 hrs	End of treatment
Average ..	58.5	839.2	783.5	686.2	595	268.5	167	186.6
Maximum ..	116	1066	1000	955	700	322	200	255
Minimum ..	44	678	578	478	490	200	134	150

TABLE III

	Initial		1st week		2nd week		3rd week	
	SI	TIBC	SI	TIBC	SI	TIBC	SI	TIBC
Dimorphic anaemia (27 cases)	83.4 (28-245)	403.6 (200-744)	183.2 (67-455)	372.07 (300-488)	253.7 (72-389)	325 (233-499)	126 (78-150)	348.1 (221-500)
Microcytic anaemia (18 cases)	57.4 (33-155)	399.9 (210-600)	191 (94-300)	355.4 (222-465)	138.8 (56-233)	419 (289-477)	199.9 (67-372)	426.7 (333-500)

TABLE IV

	Total protein in Gms%	Albumin	Globulin	Alpha 1	Alpha 2	Beta	Gamma
Non-pregnant	7.40	4.04	3.36	0.35	0.70	0.92	1.39
Pregnant normal	6.43	2.37	4.06	0.60	0.92	1.14	1.40
Anaemia in pregnancy	5.54	2.34	3.20	0.43	0.67	0.90	1.20

of treatment was completed. Table V gives the average, minimum and maximum weekly response obtained in the two different types of anaemia.

For every 100 mgms. of Jectofer administered a rise in haemoglobin of 0.2 gm.%, 0.23 gm% and 0.26 gms.% was obtained in the first, second and third weeks respectively. The average daily rise in haemoglobin was 0.23 gm.% with a range of 0.02 gm.% — 0.38 gm.%. The peak reticulocyte response occurred a week after commencement of therapy, the maximum obtained being 20%.

TABLE V

	Initial		1st week		2nd week		3rd week	
	Hb%	PCV	Hb%	PCV	Hb%	PCV	Hb%	PCV
Dimorphic	3.9 (1.8-6.3)	17 (9-26)	5.7 (3.6-8.1)	23.5 (15-30)	7.2 (3.6-10.1)	28.6 (16-38)	8.8 (7.2-11.2)	31.6 (27-39)
Microcytic	3.8 (2.1-6.7)	18.5 (11-26)	5.3 (3.1-7.4)	23.5 (15-29)	7.06 (5.3-9.5)	29.8 (21-32)	8.15 (6-9.2)	30.7 (25-35)

The average iron deficit in this series of patients was 1700 mgms. (700-2200 mgms.) and average period of hospitalisation three weeks. The total iron injected as Jectofer was 100,800 mgms. and the number of injections 1008. Two patients with severe anaemia (haemoglobin 2.5 gms.%) developed congestive cardiac failure during therapy. These were treated by exchange transfusion and later, the therapy with Jectofer was continued. Congestive cardiac failure is not an uncommon feature in patients with severe anaemia in pregnancy specially when packed cell volume falls below 12% and haemoglobin less than 2.5 gms.%. It has been our practice to treat such cases with exchange transfusion to tide over the immediate crisis and then follow it up with conventional iron therapy. The congestive cardiac failure in these two cases was not due to Jectofer. On the other hand these patients responded very rapidly to Jectofer injections after the exchange transfusion.

In four patients no improvement was found in spite of a full course of Jectofer injections. Their details are given below:

These 4 cases had to be treated with repeated blood transfusion. Except in case No. 4 the average serum protein was on a par with those who responded well. The serum proteins were abnormally low in case No. 4.

Toxic reaction

Total number of patients — 60.
Total number of injections — 1008.
Total iron given — 100800 mgms.

Reactions

Generalised — 0.
Nausea and vomiting — 9.
Excessive salivation and sneezing — 1.

No. Type of anaemia	Hb g%	PCV %	Serum iron gamma %	TIBC gamma %	Total proteins g%	Albumin	Globulin	Alpha 1	Alpha 2	Beta	Gamma
1. Microcytic (normoblastic)	5.6	20	39	345	—	—	—	—	—	—	—
2. Dimorphic (normoblastic)	2.1	11	56	500	5.4	1.98	3.42	.31	0.67	1.09	1.35
3. Microcytic (normoblastic)	6.7	25	Lysed	333	5.93	2.43	3.5	0.37	0.66	1.03	1.44
4. Dimorphic (normoblastic)	5.9	20	200	265	4.5	1.87	2.63	0.35	0.53	0.76	0.99

Pain in the neck and upper limbs — 1.

Nausea and Vomiting

It occurred in 9 patients and in all within 10 minutes of the injection. None vomited more than once. The vomiting recurred at the second injection also but not after. Chlorpromazine 25 mgms. given orally prior to the injection controlled vomiting. In three patients, in association with vomiting, there was a rise in blood pressure. From an initial level of 100/70-130/90 mm. of Hg. it rose in two to 150/100 after the injection and in one to 180/100 mm. of Hg. These reactions were transient returning to normotensive levels within an hour.

Excessive Salivation and Sneezing

It occurred in one patient 15 minutes after the injection. The sneezing lasted for nearly half an hour. Chlorpromazine helped to control it.

Pain in the Neck and Upper Limbs

This occurred in one patient after 600 mgm. (6 injections) of Jectofer. There were no positive clinical signs. The pain was rather severe and the patient refused further injections.

Slight staining of the skin was observed in one patient. "Black urine" was not voided by any one in this series.

One of the patients in this series had been treated with "Imferon" in her previous pregnancy during which she developed severe muscle and joint pains with pigment spots in the skin of both lower extremities and inguinal lymphadenitis. Biopsies of the pigment spots and the gland were positive for iron. Her symptoms improved when imferon was discontinued. Two years later, in this her present pregnancy she was treated with Jectofer; she had a total of 1000 mgms. with no reaction and good response.

Discussion

The intramuscular administration of iron has been increasingly applied since Fletcher and London (1954) produced their iron dextran complex. Baird and Padmore (1954) and others studied its clinical properties and found it to give good therapeutic results. Menon and Willmott (1960) used in anaemia in pregnancy and obtained satisfactory therapeutic results. However, they observed certain toxic reactions in 16.9% of cases which could not be ignored. Severe nausea and vomiting, muscle and joint pains, serious enough to incapacitate the patient, effusions into joints, encephalopathy were some of the reactions noticed. In fact one patient died of cerebral haemorrhage and with reluctance it was concluded that Imferon was not without serious side-effects when used in the treatment of especially dimorphic anaemia in pregnancy.

Many reports on Jectofer indicate its quick absorption from the site of injection as demonstrated by a sharp rise in the serum iron concentration. Our studies on 4 patients confirm these findings, slight variations in the response to treatment have been reported. But in general using Iron sorbitol an increase in haemoglobin of 0.3 gms. % per 100 ml. of blood has been reported (Aderson 1961). Our trials showed an increase of 0.23 gm. % 100 ml. of blood. This lower-

ed value may be due to the fact that all our assessment has been made in pregnant women suffering from a severe degree of anaemia. We have always obtained, using iron intravenously or intramuscularly, a lower response rate in pregnant women than in the non-pregnant.

One of the advantages of iron sorbitol is said to be the absence of toxicity and side-reactions. Almost all reported reactions are mild and minimal. Of these pain at the site of injection is the commonest. Mild nausea and vomiting and staining of the skin have also been reported. Scott (1962) reported three moderately severe reactions but is of the opinion that they were avoidable ones. In our experience there has been no serious reactions. The nausea and vomiting in 9 cases, within 10 minutes of the injection, passed off quickly and did not require further attention. In three of these patients there was associated rise in blood pressure which returned to normotensive levels within an hour. We have observed such rises using iron dextran also. Four cases did not respond to treatment in spite of the whole iron deficit being given as Jectofer. There were no obvious aetiological factors in these cases. The cause of this non-response is not understood.

It is observed that "Jectofer" gives a satisfactory therapeutic response in the treatment of severe anaemia in pregnancy and that side-reaction and toxicity resulting from its use are only slight and not serious.

Summary and Conclusion

1. Sixty pregnant women suffering from severe anaemia in pregnancy were treated with "Jectofer".

2. Prior to treatment a complete haematological investigation including bone-marrow biopsy, estimation of serum iron, total iron binding capacity and serum proteins by electrophorosis were done. These estimations were repeated during therapy and at the end of treatment.

3. On an average for every 100 mgms. of Jectofer administered a rise in Hb. level of 0.23 gm. % was obtained; 4 cases failed to respond to treatment.

4. No serious side-reactions were met with. The observed reactions were mild.

5. It is concluded that Jectofer gives reasonably satisfactory therapeutic response with minimal side-reactions when used in the treatment of severe anaemia in pregnancy.

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References

1. Anderson, N. S. E.: Brit. Med. J. **2:** 275, 1961.
2. Anderson, N. S. E. and Bergstrom, I.: Srenska Lak-Tidn **53:** 13, 1956.
3. Baird, I. M. and Podmore, D. A.: Lancet. **2:** 942, 1954.
4. Fletcher, F. and London, E.: Brit. Med. J. **1:** 584, 1954.
5. Lindvall, S. and Anderson, N. S. E.: Brit. J. Pharm. **17:** 358, 1961.
6. Menon, M. K. K. and Willmott, Mary: J. Obst. & Gynec. Brit. Comm. **67:** 804, 1960.
7. Nissin, J. A.: Lancet **2:** 49, 1947.