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INTRAMUSCULAR IRON IN NON-EUROPEAN PREMATURE INFANTS

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Iron depletion is liable to occur in the premature infant before the age of 4 months and unless substantial amounts of iron are absorbed, iron deficiency anaemia is said to be inevitable.[1]

Oral preparations of iron may prevent this, but little iron is stored by the body and it has to be given continuously, for at least the first 12 months, if the haemoglobin is to be kept at a reasonably high level. In a population which cannot be relied upon to carry out such prolonged treatment, this method will probably be unsuccessful.

Gaisford and Jennison[2] reported in 1955 on the intramuscular treatment of anaemic infants with the iron-dextran complex, 'imferon'. They also studied its prophylactic value against the anaemia of prematurity. Ten premature babies were each given 150 - 250 mg. of imferon, according to weight, at 3 weeks of age. The effect on the haemoglobin level was contrasted with that in 10 comparable babies not receiving iron supplements.

The authors found that at 16 weeks of age those babies who had received imferon had substantially higher haemoglobin levels than the control cases. The difference was maintained and increased until the 24th week, the last date reported in the article. At that time the average haemoglobin level in the imferon group was 82·2% (12·3 g. per 100 ml.), and in the untreated group 65·6% (9·9 g. per 100 ml.).

We decided in 1957 to repeat this trial on non-European babies in the premature unit at the Red Cross War Memorial Children's Hospital, Cape Town, to see if Gaisford's results could be reproduced. In this instance the babies were to be followed until the end of their first year to find out whether anaemia could be prevented, at any rate until this time.

Babies in this unit are born at home and are usually only accepted up to 48 hours after birth. In the group of infants to be discussed, most were within a few hours of birth, and all were less than 48 hours old when admitted, with the exception of one baby who was 4 days old and a pair of twins 7 days old when taken into hospital.

METHODS

Babies were selected by random sampling, either to receive imferon at 4 weeks of age, or to get no iron supplements. There were 38 cases in the first group and 35 in the second. The dosage of imferon was 150 mg. given as 50 mg. (1 ml.) daily for 3 successive days. A few babies were given 250 mg. spread over 5 days.

After these infants were discharged, their mothers were asked to bring them back to hospital for monthly follow-up examinations until the babies reached their first birthdays. At these visits the babies were weighed and their haemoglobin was estimated by the pathological service of the hospital, using a Klett-Summerson colorimeter. The infants were examined for, and enquiry made about, any infections since the previous visit. An approximate estimate of the physical and mental development was also recorded.

As far as could be determined, additional iron was not given to the babies after they had left hospital during the period of study, except in the case of the pair of twins who both received some oral preparation of iron for a while. As will be seen, this had little effect on their haemoglobin levels.

It was difficult to get mothers to bring their babies back regularly for a whole year and when it was decided to terminate the study, 2¼ years after its commencement, only 12 infants in each group had attended for the whole 12 month period required for the study. Of the rest some had died, but the great majority just failed to return for follow-up examinations, despite frequent letters from the social worker.

What follows, therefore, is a comparison between 12 babies who had not received iron supplements and 12 who had been given intramuscular iron. Nine of the latter had received 150 mg. of imferon and 3 had had 250 mg.

With so few cases, the results can do no more than indicate trends and should be considered in that light.

RESULTS

Table I gives the mean haemoglobin level in each group at intervals during the first 12 months of life. The levels are also shown in graphic form (Fig. 1).

TABLE I. MEAN HAEMOGLOBIN (G.%) DURING FIRST YEAR

Treatment	*Cases*	*Initial level*	*Level at age (in months)* 2	4	6	9	12
1. No iron ..	12	18·6	9·8	9·4	8·4	8·2	7·6
2. Imferon 150 mg. ..	9	18·7	9·3	10·0	9·9	9·7	9·2
3. Imferon 250 mg. ..	3	21·5	9·3	11·4	11·1	10·0	9·6
4. Combined imferon (lines 2 and 3) ..	12	19·4	9·3	10·4	10·2	9·7	9·3

Initial Hb. difference between 1 and 4 is not significant. $P > 0{\cdot}50$.
12-month Hb. difference between 1 and 4 is significant. $P < 0{\cdot}05$.

In the infants who received no supplementary iron there was a continuous fall in haemoglobin values throughout the year, reaching a mean level of 7·6 g. per 100 ml. at 12 months. Only 3 of the 12 babies had a haemoglobin of over 9 g. per 100 ml. at this time.

In the imferon-treated group, after a steep fall in haemoglobin at 2 months, which appears inevitable, there was a rise at 4 months, which was fairly well maintained

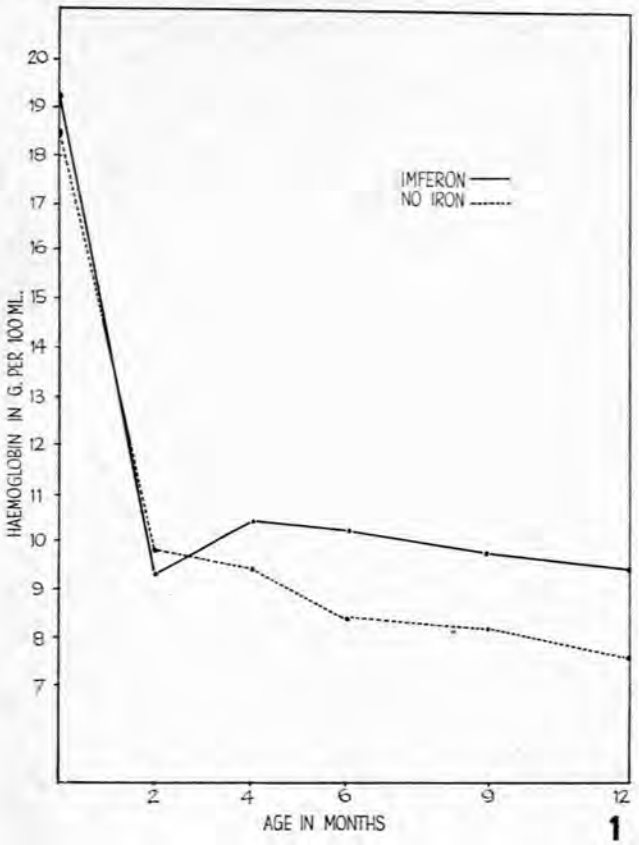

Fig. 1. Mean haemoglobin levels in premature infants. Twelve patients received imferon and 12 received no iron supplements.

to 6 months. Thereafter a gradual fall occurred to a mean level of 9·3 g. per 100 ml. at 1 year, but even at 4 months our figures were well below those reported by Gaisford and Jennison.[2]

The 3 babies who had been given 250 mg. of imferon were successive cases drawn for iron therapy and there was no selection on account of weight. By chance this was well distributed, being 2 lb. 15 oz., 3 lb. 7 oz., and 4 lb. 12 oz. respectively. Up to 6 months their mean haemoglobin figures were rather higher than those in the babies who had had 150 mg. of intramuscular iron. At 9 and 12 months, however, the figures in the 2 groups were not greatly different, and in the last line of Table I the haemoglobin levels for all 12 babies on imferon are combined.

In 9 additional patients in each group who attended only to the end of 4 months, the same haemoglobin differences at this time were found as in the groups completing the full 12 months' study period.

The figures in our pair of twins are of interest (Table II). The card drawn for the first twin was 'no iron' and the other was thereupon deliberately put into the imferon group in order to be able to compare results. At this time 250 mg. was being given and the second twin received that amount. The table illustrates once more the continuous fall in haemoglobin when no iron is given. By

TABLE II. TWIN BABIES

Patient		Initial level	Level at age (in months) 2	4	6	9	12
Charles J. No iron	Hb. (g.%)	18·5	10·7	9·1	8·1	7·4	6·4
	Wt. (lb./oz.)	3/3	5/3	9/13	12/11	15/8	18/3
Calvin J. Imferon 250 mg.	Hb. (g.%)	17·0	9·3	13·4	11·1	9·6	10·7
	Wt. (lb./oz.)	2/15	5/7	10/0	12/13	16/4	18/6

the end of the year there was a haemoglobin difference of 4 g. per 100 ml. in the 2 babies.

Mental defect, severe in 5 patients, appeared to be present in 12 of the 24 babies in the study. This was unrelated to the giving or withholding of iron but was found in those who had the lowest initial weights. All 12 weighed less than 4 lb. when first seen. This is in line with current opinion which suggests that the smallest babies at birth run the greatest risk of mental defect subsequently (Knobloch *et al.*,[3] Dann *et al.*,[4] Drillien[5]).

DISCUSSION

Other Studies

Hillborg and Nilsson[6] reported the use of imferon in premature babies in Sweden. As in our cases, those who were given imferon had a higher haemoglobin level at 4 months than those who had not received intramuscular iron. Their cases had a mean figure at that time of a little over 12 g. per 100 ml. and this level was maintained to the end of 12 months. Imferon dosage was 100 - 200 mg., most babies getting 150 mg. It is not possible to compare their cases where no imferon was given, with ours, as oral iron was given to the Swedish patients if the haemoglobin at any time fell below 11 g. per 100 ml. Their figures for 4 and 12 months remained in the region of 11 g. per 100 ml.

Hammond and Murphy[7] did a similar study in San Francisco. They used 100 mg. of imferon and from the third month found a highly significant difference in favour of the imferon-treated group (11·9 g. per 100 ml. compared with 10·5 g. per 100 ml.). This difference was maintained until 12 months and the authors' conclusion was that iron given in the neonatal period is able to prevent the late anaemia of prematurity. The article contains a comprehensive review of prematurity anaemia.

Reasons for Disappointing Results

In our patients on imferon the mean haemoglobin figure at 12 months was 9·3 g. per 100 ml. and in those who had not received iron supplements it was 7·6 g. per 100 ml. Despite this difference, which is a significant one, the figure of 9·3 g. per 100 ml. is disappointing and it cannot be said that the late anaemia of prematurity was entirely prevented. What is the likely reason for this?

Quantity of Imferon

Was too little imferon given? Gairdner[1] suggested that a baby needs about 245 mg. iron in his first year to supply growth requirements. Our 3 patients who were given 250 mg. imferon did not seem to do better than those who received only 150 mg. Hillborn and Nilsson[6] gave much the same dosage as we did and Hammond and

Murphy[7] smaller amounts, but in both groups their 12-month haemoglobin figures were well above ours.

Influence of Birth Weights

Did birth weights influence our figures? Were there, for instance, many babies in our imferon group with very low initial weights and did this affect the issue? Only 4 of our patients weighed 3 lb. or less and their mean haemoglobin at 12 months was 9·4 g. per 100 ml. At the other end of the scale, there was only 1 baby of over 4 lb. in the group and his 12-months' reading was 7·7 g. per 100 ml. Our initially smallest babies, therefore, did not have the lowest haemoglobin readings at 1 year.

It was noted, however, that whereas the group on imferon had a mean starting weight of 3 lb. 5 oz. compared with 3 lb. 10 oz. in the 'no iron' group, the mean weights of these groups at 1 year were 19 lb. 4 oz. and 16 lb. 6 oz. respectively. It is possible that the iron supplement may have improved the general metabolism of the recipients resulting in a better weight gain than that in the other group. The group on imferon presumably had the greatest increase in blood volume. Did those babies in the imferon group with the greatest weight gain have the lowest final haemoglobin levels? This certainly seemed to be the case in our 2 babies who had the greatest gain in weight. Each gained about 20 lb. in their first year and their final haemoglobin readings were 7·7 and 7·4 g. per 100 ml. On the other hand, 2 other babies gained just over 16 lb. each and their 12-month haemoglobin figures were both over 12 g. per 100 ml. The rest, who gained between 14 and 15 lb. had figures varying from 6·2 - 11·8 g. per 100 ml. with a mean of 9·4 g. per 100 ml. It did not seem, therefore, that weight gain kept the final haemoglobin figures down and, in any case, there were only 2 of the 12 babies who had a large weight gain. Admittedly there were only 12 cases, so perhaps one should not make too much of the above figures.

Infections

What about infection? Gaisford and Jennison[2] pointed out that this could nullify the effects of imferon and quoted one of their anaemic premature babies who had an initial rise of haemoglobin but, following an attack of bronchitis, this fell by 10%. Wintrobe,[8] on the contrary, has stated that infections lasting less than a month are not in most cases accompanied by significant anaemia. Lanzkowsky[9] found that when imferon was given to anaemic babies suffering from a coincident short-lived infection, such as pneumonia or gastro-enteritis, the iron was utilized and there was no interference with haemoglobin synthesis.

Most of our patients getting imferon had at least one infection and some several, during their first year. These infections were usually either gastro-enteritis or a respiratory infection and though some cases were severe, most were of quite short duration. Two of the 12 babies had only minor infections and it may be of significance that at the end of their first year they had the highest haemoglobin levels of all the babies, namely 12·4 and 11·8 g. per 100 ml. Each had received 150 mg. of imferon. Six more suffered from several infections, which, in nearly every instance, were followed by a drop in haemoglobin level. However, each of the 4 remaining patients had an infection between 9 and 10 months of age and in all of them the haemoglobin at 12 months was higher than at 9 months. It is difficult, therefore, to assess the effect of infection in our cases and it will require much larger numbers to determine the correct answer to this question.

Other Reasons

Is there any other reason to account for our figures not being higher at 12 months than they were? It is of interest to compare Lanzkowsky's[9] haemoglobin findings at 12 months in healthy full-term non-European children in Cape Town. The mean levels were 9·57 g. per 100 ml. in Coloured and 9·84 g. per 100 ml. in African babies. The corresponding figure for European babies in this series was 11·20 g. per 100 ml. The figures for non-European full-term babies at 12 months, who had received no particular iron supplements, are rather similar to the present series for premature infants given imferon. All that imferon seemed to have done was to bring the haemoglobin level of the premature babies up to a figure near to that of their untreated full-term counterparts, and emphasizes the anaemia which Lanzkowsky[9] has shown to be so common in non-European babies in Cape Town.

SUMMARY

Late prematurity anaemia is inevitable without the addition of iron supplements. In a population, which could not be relied upon to take oral preparations for a prolonged period, an attempt was made to prevent iron deficiency anaemia by giving intramuscular iron in the first weeks of life.

Although this resulted in better haemoglobin levels than in the untreated cases, the results were not very satisfactory as regards the prevention of anaemia, and even at 4 months our figures were well below those of other published series. It is difficult to be sure of the reason for this, particularly as it was not possible to get a large number of patients to cooperate in the study for a full 12 months.

The mean haemoglobin level at one year was similar to that found by Lanzkowsky[9] for healthy full-term non-European babies of the same age in Cape Town, and this may be a reflection of the general tendency to anaemia in the non-European children in this city.

The relation of infection to the drop in the haemoglobin level in this study was uncertain.

ADDENDUM

Is Imferon Dangerous?

Since this paper was completed a disturbing Leading Article now well known, appeared in the *British Medical Journal*.[10] In it the suggestion was made that imferon might be carcinogenic in man and the Journal recommended that the makers should withdraw the preparation.

The Leading Article was based on reports of experiments in rats and mice which were repeatedly injected with massive doses of imferon in the same site for a prolonged period.[11,12] A considerable number of the animals developed sarcomas.

Several letters to the Journal followed, notably one by Golberg[13] of the research department of the firm manufacturing imferon. He stated that, under similar conditions,

many preparations, including glucose, fructose and arachis oil were carcinogenic. He had been able to produce some sarcomas in mice by similar heavy dosage of imferon, but found only one in 50 hamsters so injected and none in rabits or guinea pigs. Golberg believed that, in the affected animals, repeated trauma and muscle necrosis at the site of the injections was more likely to be the cause of the sarcomas than was the imferon. He reported that skin sections from patients who had received subcutaneous injections of imferon showed almost total disappearance of iron after 23 days. Golberg maintained that although sarcomas could be produced in some laboratory animals, it was not logical to state that the same might therefore occur in man.

A further letter appeared in the *British Medical Journal* in June 1960[14] signed by 7 distinguished physicians; this carried considerable weight. The joint opinion of the signatories was that imferon, in the recommended dosage, carried a negligible risk and was probably less hazardous in other respects than intravenous iron or blood transfusion. Practitioners could, therefore, in their opinion, use the drug without fear.

The whole matter has aroused considerable interest and perturbation and has been reviewed in editorials in the Australian,[15] American,[16] and Canadian[17] medical press. The consensus of opinion of these journals was that, if given in the correct dosage and with circumspection, imferon is a valuable agent. All gave it as their opinion that the evidence for its toxicity was hardly convincing.

Here the matter rested until 27 August, when the *British Medical Journal* published an article by Robinson *et al.*[18] from Vancouver, Canada. This described a soft tissue sarcoma in the left deltoid region of a 74-year-old woman at the alleged site of imferon injections given 3 years previously. It was not claimed that the tumour was definitely caused by the imferon, especially since the sarcomas produced in rats by this method differed considerably in appearance. Nor could the authors say with certainty that the tumour in their patient was a primary one. Nevertheless it was suggested that imferon might possibly have been the carcinogenic agent.

The same issue of the Journal carried an Annotation[19] which reaffirmed the Journal's previous attitude, especially in view of the abovementioned case. A letter by Prof. A. Haddow in the same number[20] was also discussed in the Annotation. This letter pointed out that the risks of imferon would not be known for about 15 years from the time it was first used. In the meantime Haddow felt that it is not justifiable to assert that the preparation carries a negligible risk in man.

The latest word on the subject is a memorandum by Benger Laboratories Ltd., the manufacturers of imferon. This reports discussions between Dr. Golberg of Bengers and Dr. J. P. Smith of the Christie Hospital and Holt Radium Institute, Manchester, on the one hand, and the Canadian authors of the article mentioned above on the other. There would appear to be some doubt whether the patient did, in fact, receive imferon in her upper arm. Even if this was the case, the relation of imferon to the tumour is questioned, both because of the short latent period, and because of the histological appearance, which differed from that occurring in animals who had received excess dosage of intramuscular iron. It must, however, be stated that there may be a species difference in the histological appearance of the tumours.

Reports indicate that more than 1,000,000 persons have received imferon during the last few years. What are the harmful effects reported? One case of sarcoma in a 74-year-old patient with an unproved relationship.

It appears to me that the risk of imferon is little greater than is the case with other agents such as chloramphenicol, chlorpromazine and even penicillin. These drugs have not been withdrawn. Why then should imferon? Aplastic anaemia, liver disease and anaphylactic shock from the above drugs may all cause death, but the word 'cancer' probably still strikes more terror into the heart of the public than does any other. It is necessary, therefore, to have a balanced viewpoint in the case of imferon.

If there is a risk it should be a calculated one, and in this case it is to my mind so small as to be, in fact, negligible.

I have the authority of Prof. F. J. Ford, Head of the Department of Child Health at the University of Cape Town to state that it will be the Department's policy not to discourage the use of imferon provided it is not used indiscriminately. The chief indications for its use in paediatrics are the prevention of iron-deficiency anaemia in premature babies, and the treatment of this anaemia in infants and older children, but only in cases where the parents cannot be relied upon to give iron by mouth, or in the rare cases where oral iron cannot be tolerated.

As regards the efficacy of imferon there can be no doubt.

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