Annotation: Total Dose Intravenous Infusion of Iron Preparations

Talking of parenteral iron therapy for iron deficiency anaemia (IDA); particularly as total dose infusion (TDI) intravenously with its known benefits like compliance, certainty of total dose administration, calculated/ expected response and more so curtailment of need for blood transfusion; undoubtedly the current products like ferrous sucrose complex (Venofer) are an improvement over the former ones like Ferrous Iron Dextran Complex (Imferon), as far as the rapidity of action and greater safety are concerned.

Furthermore in Obstetrics TDI of iron preparations postpartum (like in the article on page 223 of this issue), has parameters almost similar to antepartum/antenatal administration.

But to label the formerly used products like Iron Dextran Complex as notoriously associated with significant risk of so called 'anaphylactoid' reactions; and that too without referring to any meta-analysis of authenticated multi center trails; needs some evaluation and explanation, just to maintain such issues in the right perspective.

This venture reminds me of the initial days of use of Iron Dextran Complex, when I conducted projects on it from 1963 onwards.

I. Lagos Series

While stationed at Military hospital, Yaba, Lagos, Nigeria, I conducted a pilot project on Nigerian pregnant women.[1] It is worth noting however that iron deficiency was rare in Nigerians, yet I could confirm by laboratory support IDA in 70 of them, around 34 wks of pregnancy. In when the essential prerequisite was to exclude any history of allergies in particular that of asthma.

Total calculated dose of Imferon was administered by intravenous infusion by and large in line with the routines of Basu from India[2] after a personally supervised test dose with diluted solution over half an hour. No patient developed any adverse reaction except one lady who had somehow failed to disclose history of asthma and went into ananphylaxis, while I was still by her side. With all emergency measures kept at hand, she recovered fast and was excluded from the trial.

II. Leicester Series

The next phase of the trial with TDI of Iron Dextran Complex was conducted at Leicester general hospital, Leicester, England in 1969 on 40 expectant, iron deficient, anaemic women, around 34 weeks of pregnancy. The response was good and there were hardly any reactions, which is worthy of note.

By that time, numerous leading articles had appeared on Iron Dextran Complex administration as TDI during antenatal period, in prestigious journals like the Lancet, BMJ, Journals of Obstetrics and Gynaecology from various countries like America, UK, and Australia etc. demonstrating adequacy of response with Imfron TDI as well as its safety with due precautions.[1] The incidence of IDA in Pregnancy was ample times reported to have dropped with TDI Imferon concomitant with administration of folic acid.

III. Holy Family Hospital (HFH) Rawalpindi Series

Back at home at HFH, Rawalpindi a similar study was carried out on 786 cases of IDA in pregnancy in early nineteen seventies. Some cases with severe anaemia and associated cardiac decompensation were also encountered in this series, specially amongst lower socio economic group. TDI of Iron Dextran Complex was administered to all the iron deficiency anaemia cases with similar technique and all the necessary precautions, with individualized variations if and when required, like in cardiac cases.

The patients of this series, at times showed local thrombophlebitis at the site of infusion, at other times fever with rigors while arthralgic pains occurred in those who had a tendency from such pains already, increased tendency for haemorrhages if they otherwise had to occur and occasional anaphylactic type of reactions occured which reversed with immediate intervention.

Being surprised with these phenomena, Fisons Pharmaceutical Company was informed, which lead to withdrawal of the product for couple of months. The company modified the formula and marketed Imferon again. There after the next lot of its ampules, when given as TDI hardly ever showed any significant reaction.

Common Parameters of the three Multinational Trials

- Diluent: in all the 3 trails(Lagos, Leicester and Rawalpindi) I had used normal saline as a diluent, rather than 5% dextrose used by Basu[2] and others, because the latter formed larger molecular complexes and thus gave more reactions. The exceptions were cases of severe IDA with cardiac compromise, in whom 5% dextrose had to be used and that too carefully, for obvious reasons.

- Allergies: meticulous attention to history was a must.
- Personalized care: this was a common feature of the three series.
- Calculated dose of Imferon: this was done by Scott`s formula and total dose was administered as an infusion over 1 to 2 days (5 to 6 hours a day) depending on the total calculated dose. By and large technique of Basu[2] was followed.
- Antihistamines: no prior antihistamines were required to be given as a routine.
- Discontinuation of prior iron: oral iron was stopped for preceding 48 hours and the parenteral iron for prior fortnight as a must.
- Response: the desired haemogobin (and replenishment of iron stones was achieved over a period of six weeks (as evaluated by laboratory investigations). The response was more rapid in first 3 weeks and more so in cases with gross IDA.
- Reactions: These were not significant in adequately screened patients and exclusion of those with history of asthma, except in one case of Lagos series (already referred to). In HFH, Rawalpindi series, however, as mentioned earlier a particular batch of Imferon was detected to be the culprit in giving quite a few reactions.

- Folate: For prevention of the risk of sudden drop in folate level (being consumed by iron load) and ensuring megaloblastic anaemia, oral folic acid was administered simultaneously with TDI of Iron Dextran Complex.
- Non-Responders: To some women whose response was sluggish, particularly in Lagos and Rawalpindi series, anti-helminthiatic treatment had to be given, as well.

To get back to the administration of TDI, at HFH, Rawalpindi, Imferon was safely administrated for quite a few years, after readjustment of its formula by the company, Then suddenly it became scarcely available and other products like Iron Sorbitol Complex (Jectofer), etc appeared on the scene more vigorously.

Was it overplay of the other companies, I do not know, since I was purely interested in research and had no conflict of interest, I did not pursue the matter any further.

But the point I have made here is that unless evidence, based on genuine ethical research and meta-analysis of multi center trails confirming the adverse reaction based withdrawal of a product are quoted, it is scientifically incorrect to label a product 'notorious',

Furthermore as it is widely known that some pharmaceutical companies can maneuver to get so called 'Ghost Trails' published even in prestigious journals,[3] one has to be aware of them as well.

Lastly it is true that all clinicians with obstetricians alike, should be aware of the adversities associated with therapies – as Hippocrates said- "Lots of ailments are associated with the therapies that we give"!

Editor-in-Chief

References

- Akhtar KAK. Experiences with iron deficiency anaemia in Pregnancy. Rawal Medical journal 1976(6);5(1):11-20.
- Basu SK. Administration of iron dextran complex by continuous intravenous infusion. J, Obstet Gynaecol, Brit Cwlth 1965; 72:253-258.
- Healey D. Pharmacosis is the fourth leading cause of death. Pulse Int`l 2013 (Dec); 14(24):1-2.

Though two of the references given above are very old, in the usual sense and JSOGP does not accept references more than 5 years old except for those references pertaining to History. Thus History is History and cannot be composed of yesterday till 5 years. Per se it will be decades, centuries or more.....Thus *"Old is Gold"*