

# THE SAFETY OF IRON DEXTRAN AND A COMPARISON WITH IRON SUCROSE FOR INTRAVENOUS USE: A SHORT REPORT TO THE WORLD HEALTH ORGANIZATION ADVISORY COMMITTEE ON THE SAFETY OF MEDICINES.

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Date: 18<sup>th</sup> October 2004

## Background

1. At a meeting of the WHO Expert Committee on the Use of Essential Medicines, held some time early in 2004 or late 2003, it was decided to delete iron dextran from the WHO list of Essential Medicines. It is understood that the decision was not based on evidence, and it is assumed but not verified that the misgivings of the expert committee would have been with the safety of iron dextran administered parenterally. No replacement for iron dextran was recommended by the expert committee.<sup>1</sup> The WHO Advisory Committee on the Safety of Medicines is seeking the evidence for such a decision and recommendations for replacement of iron dextran by an alternative formulation of iron for intravenous use, provided the evidence would support such a recommendation. The formulation concerned would be likely to be iron sucrose for intravenous administration.<sup>2</sup> In preparing this report a full literature search has been conducted, and Meyler's Side Effects of Drugs 14<sup>th</sup> and 13<sup>th</sup> editions were consulted.
2. Parenteral iron is probably used too widely; there are few indications for its prescription. These include: intractable gastrointestinal intolerance to the oral product, hyperemesis in pregnancy, very severe blood loss, and possibly ulcerative colitis. A low iron binding capacity (due for example to prior saturating iron therapy or malnutrition), folic acid deficiency and an allergic constitution predispose the patient to adverse reactions to parenteral iron<sup>3</sup>.

## Safety profiles of iron dextran and of iron sucrose

3. Fletes *et al* (2001) have reported on iron dextran-related adverse drug events following intravenous iron dextran administrations in the United States between October 1998 and March 1999. Of 841 252 IV iron dextran administrations to patients with end-stage renal disease there were 165 reported suspected adverse drug events, corresponding to an overall rate of 0.000196%, or approximately 20 per 100 000 doses. 18 patients (11%) required hospitalisation and 1 patient (0.6%) died. Dyspnoea (43%), hypotension (23%), and neurological symptoms (23%) were the most common major ADEs. In summary, when used strictly for the right indication serious adverse reactions to IV iron dextran are rare. Iron dextran-related ADEs are difficult to predict.

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<sup>1</sup> Email dated March 02, 2004 from Dr Mary Couper to members of the WHO advisory committee on the safety of medicines.

<sup>2</sup> This report will not deal further with intramuscular administration of iron formulations, the use of which is becoming obsolete because of their adverse safety profile.

<sup>3</sup> Refer Meyler's Side Effects of Drugs 13<sup>th</sup> edition p596 and 14<sup>th</sup> edition p699.

4. In a web site posted statement on the safety of iron sucrose for intravenous administration<sup>4</sup>, it is clear that the overall experience with IV iron sucrose is considerably less than with iron dextran. Exposure to the drug (as Venofer) has been documented in 231 patients undergoing chronic haemodialysis in clinical trials and in 1 051 patients undergoing haemodialysis in two post-marketing safety studies. As at 10.10.2004, the safety of intravenous iron sucrose (as Venofer) had been documented in a total of 1 282 patients. Two (2) patients have experienced mild or moderate hypersensitivity reactions.
5. In a North American clinical trial of the safety and efficacy of iron sucrose for iron deficiency in patients with dialysis-associated anaemia there were no serious adverse drug reactions to IV iron sucrose in 77 enrolled patients, including those with previous iron dextran sensitivity (the number of the latter is not clear), other drug allergies, or concurrent angiotensin-converting enzyme inhibitor use (iron sucrose was administered in this study as 1 000 mg in 10 divided doses by IV push, without a test dose) (Charytan C *et al.*, 2001).
6. In a review Baillie *et al* (2000) suggest, but fail to establish, that iron sucrose and iron gluconate may have less adverse effect profiles when compared with iron dextran. They point out that additional clinical experience is required to establish the role for these new iron products (Baillie *et al*, 2000).
7. Hoigne *et al* (1998), in reviewing the experience of patients exposed to iron hydroxide sucrose complex given intravenously (altogether around 8 100 patient-years were assessed, with exposure to approximately 160 000 ampoules of iron sucrose, each containing 100 mg elementary iron) not a single life threatening reaction was observed. The authors suggest that the relatively good tolerance to intravenous iron sucrose in patients with chronic renal insufficiency may be due either to reduced immune competence in patients with chronic renal insufficiency and/or to the preparation itself, or probably both. Their findings need confirmation.
8. Faich and Strobos (1999) have reviewed 74 allergic adverse events attributed to sodium ferric gluconate complex and reported to the WHO, German Health Bureau, and the manufacturer (combined). An adverse event reporting rate of 3.3 allergy episodes per million doses per year over the period 1976 to 1996 was compared with 8.7 reported allergy events per million doses per year with iron dextran in the United States in 1996. There were no case fatality reports for sodium ferric gluconate over the entire period; for iron dextrans over the same period there was a case fatality rate of 15.8% of 196 allergy/anaphylaxis cases. The authors concluded that sodium ferric gluconate is safer than iron dextrans as an iron replacement agent. However, the difficulty with the conclusion is that the extent of use of the two preparations would have been quite different; in 1996 an estimated 3 million doses of iron dextran were given, but the figure for other iron preparations for IV use is not known.
9. Other reports attesting to the safety of iron sucrose are those of: van Wyck et al (2000) – no serious adverse drug reactions in a total of 223 doses of iron sucrose, 184 by IV push, 39 intravenously; Hudson and Comstock (2001); Nissenson and Charytan (2003) – they find that further prospective work is necessary to determine whether iron sucrose and iron gluconate are safer than iron dextran in dialysis patients; Charytan et al (2004), who found that iron sucrose is safe and well tolerated in haemodialysis patients intolerant to iron dextran or sodium ferric gluconate (there were 130 such

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<sup>4</sup> Refer: [www.rxlist.com/cgi/generic2/venofer\\_ad.htm](http://www.rxlist.com/cgi/generic2/venofer_ad.htm) (last accessed 18th October 2004).

patients intolerant to other iron preparations, none of whom suffered a serious reaction to iron sucrose); Bastani et al (2004) who describe in a retrospective study the incidence of side effects with high-dose ferric gluconate complex in sucrose (Ferlecit) in patients with severe chronic renal failure (they found that significant untoward reactions occurred in 10-30% of patients in a dose-dependent fashion – altogether 40 treatments were analysed in this study); Breymann et al (2001) who found that iron sucrose was safe given with adjuvant recombinant erythropoietin for the treatment of resistant iron-deficiency anaemia during pregnancy resistant to orally administered iron given alone; Bastani et al (2002), who found that 5 patients who had previously had a severe, potentially life threatening reaction to intravenous iron dextran preparation tolerated iron sucrose with no untoward effects; Coyne et al (2003), who found that of 143 patients who had previously been intolerant to iron dextran and were exposed to sodium ferric gluconate complex 3 had a suspected allergic event, including 1 with a serious reaction (0.7%) but there were no serious adverse events in 2 194 iron dextran-tolerant patients, and a history of dextran sensitivity also predisposed to allergic reactions to placebo in 2 patients – the results suggested host idiosyncrasy; Fishbane (2003) who in a review article suggested that iron sucrose and sodium ferric gluconate have more favourable safety profiles than iron dextran; Eichbaum et al (2003), who found no difference in the number of adverse reactions to iron dextran given by infusion (total number of reactions 20.5% of 39 infusions in 32 patients, 2.6% severe) and iron gluconate (total number of reactions 23% of 26 infusions in 4 patients, 0% severe); Chertow et al (2004) who found an estimated 94 adverse reactions reported with parenteral iron preparations, but no significant difference between the different formulations of iron (high molecular weight iron dextran, lower molecular weight iron dextran, and sodium ferric gluconate complex) – they point out that head to head comparative clinical trials have not been conducted.

### **Mechanisms and risk situations**

10. It would be important to know whether the basis of the severe adverse allergic reactions experienced with iron dextran are attributable to the dextran component. If that were the case, formulations without dextran might be expected to be safer. However, the situation is not that clear. The following is understood:
  - i. Patients with a history of allergy may be at risk of developing undesired immunological reactions such as asthma attacks, following parenteral iron administration; however, the incidence of such reactions seems to be low, and the risk probably also exists with other iron compounds as well (Meyler 14<sup>th</sup> edition, page 701).
  - ii. Iron toxicity may be expected if the amount of free iron that is released into the plasma exceeds plasma iron-binding capacity (this is more likely to occur when using iron sorbitol – citric acid complex (iron sorbitex), since the iron is less firmly bound than with iron dextran (Meyler 14<sup>th</sup> edition, page 701).
  - iii. Several conditions associated with low iron-binding capacity such as malnutrition and previous or simultaneous oral iron therapy appear to predispose to these toxic reactions. In addition, folic acid deficiency has been reported to be a predisposing factor (Side Effects of Drugs, Annual 9, 516); the likely mechanism here is a disturbance of iron utilization secondary to folic acid deficiency that results in an increased saturation of iron-binding capacity.

- iv. Different parenteral iron formulations differ experimentally in their comparative toxicity and potential for cytotoxicity in a manner that is related directly to the potential of the iron contained in them to cause free radical generation and severe adenosine triphosphate depletion; iron sucrose has greater potential for that than iron dextran (Zager et al, 2002).

## Conclusions and recommendations

11. In the absence of head-to-head comparative clinical trials it cannot be stated with confidence that iron sucrose (or any other formulation of iron for intravenous administration) is clearly safer than iron dextran. At least part of the negative safety record of iron dextran is linked with its extensive use over the past 30 to 40 years. From this record it can be said that the incidence of severe adverse effects is roughly quantifiable, and is not negligible (*vide supra*). The outcome of anaphylactic reactions to iron dextran is occasionally fatal. Although fatal anaphylactic reactions to iron sucrose do not appear to have been described, and they have been with iron dextran, this does not necessarily mean that they would not occur in comparable numbers if the extent of use of iron sucrose and iron dextran, respectively, were similar.
12. Although dextran itself is immunogenic, and potentially responsible for allergic reactions including anaphylaxis and anaphylactoid reactions, the mechanism(s) of toxicity of iron dextran are not necessarily attributable to its dextran component. Equally, or more, likely would be the availability of free iron after administration.
13. Comparisons of the safety of iron dextran for intravenous administration with other iron formulations do not allow of a clear recommendation in favour of iron sucrose, even though it might be argued that there is a *prima facie* case. It is noted that in a number of publications the authors suggest that further work would be necessary for this matter to be resolved.
14. In general, intravenous (and other parenteral) administration of iron appears to be excessive and not justified by the indications, which are strictly limited. A public health initiative aimed at reducing the number of severe adverse reactions to parenteral iron would require a stricter approach to the indications for use of parenteral iron administration.

## Acknowledgment

The author is grateful to Joe Talmud, Medicines Information Centre of the University of Cape Town, for his assistance in compiling the background literature for this report.

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