Labile iron in parenteral iron formulations: a quantitative and comparative study

Sir,

The recent paper by Van Wyck et al. [1] examined in vitro transfer of iron from iron products to transferrin. The discussion appears to have missed several relevant points. First, the wide concentration range examined appears not to be clinically relevant for all products. As mentioned in the Methods section, ferric gluconate has a far lower peak concentration (1900 mcg/dl after 125 mg) than iron dextrans (3080–3396 mcg/dl after 100 mg) or iron sucrose (3000 mcg/dl after 100 mg). Similarly, the peak concentration for 62.5 mg of ferric gluconate is significantly lower than the peak concentration after 50 mg of iron dextran or iron sucrose, yet these lower doses when given once every week or two to haemodialysis patients, are most likely to match ongoing iron losses [2]. When these concentrations are analysed in the authors’ Figure 1 (see attached Figure 1) it becomes apparent that one would predict little clinical difference between these products even though 25% more ferric gluconate is being administered. In figure 2 of their paper the authors excluded from their analysis the 865 mcg/dl results, yet this is very close to the peak concentration obtained after 62.5 mg of ferric gluconate (965 mcg/dl), and would likely be close to the peak serum concentration of 25 mg of iron sucrose or iron dextran.

Additionally, the discussion does not mention or discuss the wide variation in serum half-life of the iron products (1 h for ferric gluconate, 6 h for iron sucrose and 48–60 h for iron dextran). A long serum half-life would influence the time for continued iron donation, the peak drug concentration achieved, and have serious implications for administration of higher than approved doses of these products. In spite of the risk of anaphylaxis, iron dextran is still used in the US for total dose infusions (~1000 mg given over 2–3 h) for convenience reasons. Van Wyck et al. have stated that 500 mg of iron sucrose can be administered safely over 4 h. While others and I have found 250–500 mg of ferric gluconate infused over 1 h well tolerated in haemodialysis patients, we recommended only the 250 mg dose [3]. Based on the present study results alone, perhaps higher dose infusions should not be recommended at all, or if necessary the agent with the shortest half-life and lowest peak concentration should be used.

On a more clinically pertinent note, the authors state that the Scandinavian Hemoglobin Normalization Trial results support the safety of iron sucrose because the high

Fig. 1. Relationship between the change in Tf-bound iron (Delta Tf-Bound Iron) and concentration of added iron for each of four iron formulations. The two iron dextrans examined include iron dextran-I (INFeD®) and iron dextran-D (Dexferum®). Each data point represents the mean of six replicate experiments. (1) reproduced with permission from the ERA–EDTA.
haemoglobin arm received ~80 mg per week of i.v. iron and did not have a higher mortality than the lower haemoglobin group. An alternative interpretation is that the higher dose of iron sucrose led to unrecognized excess mortality that negated the benefits of anaemia correction. The authors also state that there has never been harm related to labile iron. However, there have never been studies designed to evaluate this. There are human data showing in vivo injury likely due to labile iron, including the association of accelerated atherosclerosis with i.v. iron dose [4], reduced forearm blood flow due to endothelial dysfunction after i.v. iron [5], and oxidation of lipids [6] and proteins [7] after standard doses of i.v. iron, and polymorphonuclear cell dysfunction after 300 mg of iron in peritonal dialysis patients [8].

Perhaps the best conclusion that can be made from these in vitro results is that clinical studies and in vivo studies can better address the safety of i.v. iron.

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Reply

Coyne proposes that peak plasma levels achieved after i.v. injection of ferric gluconate are half those of other i.v. iron agents, that the effect of labile iron in i.v. iron agents is attenuated by a short plasma half-life of ferric gluconate, that ferric gluconate can be infused more rapidly than iron sucrose, that high-dose infusions may not be safe for any i.v. iron agent, and that in vitro results have no bearing on the safety of i.v. iron administration in patients. Each point warrants discussion.

I.v. iron agents are colloids which, when injected intravenously, are distributed in the plasma space, so that the calculated initial volume of distribution roughly approximates plasma volume. This is true for iron sucrose [1] and iron dextran [2]. The reported finding that ferric gluconate achieves a peak plasma concentration only half of that expected prompts the conclusion that the agent is distributed in a volume equal to twice the plasma volume [3]. The resulting conclusion that 50% of the iron in ferric gluconate immediately dissociates from the compound and exits the intravascular space seems quantitatively implausible (our estimates would suggest 5–7%). Qualitatively, however, the pharmacokinetics of ferric gluconate support our finding that the labile iron fraction in this agent is not inconsiderable and may be clinically important early after i.v. administration.

Iron donation from i.v. iron agents to transferrin takes place immediately [4]. Prolonged exposure of agent to plasma leads to greater degrees of iron donation [5]. Thus, a short plasma half-life would not affect early iron donation. Rapid cellular uptake may limit late iron donation in plasma only to augment the intracellular manifestations of labile iron to which Coyne alludes.

Reactions consistent with a labile iron pathogenesis afflict 30% of patients administered 500 mg ferric gluconate i.v. over 5 h and 10% of patients given 250 mg i.v. over 3·4 h [6]. Administration of 200 mg of iron sucrose i.v. over 5 min is well tolerated [7], as is administration of 200 mg i.v. over 2 min [8]. Iron dextran has been given as aggressively as 250–500 mg over 5·10 min without evidence of labile iron reaction [9,10]. Our results showing the relative bioactivity of i.v. iron agents (ferric gluconate > iron sucrose > iron dextran) suggest that labile iron may play a role in limiting the maximum tolerated dose and rate of infusion (ferric gluconate < iron sucrose < iron dextran). The observation that in vitro results may lack in vivo correlates does not necessarily diminish their significance. In vivo i.v. iron studies that are comparative and carefully executed [5,11–13] identify potential new areas for investigation in patients, confirm that manifestations of labile iron follow the relative sequence ferric gluconate > iron sucrose > iron dextran, and lend appropriate caution to the administration of i.v. iron agents.

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