High dose of bolus iron vs low dose of weekly infusion: bolusing high dose, a recipe for iron toxicity?

Sir,

We read with interest the article by Kosch et al. [1] comparing the i.v. infusion of iron sucrose with iron gluconate in patients on haemodialysis. Although this study provides some direct comparative analysis between two forms of parenteral iron compounds, the implication that iron sucrose being a monthly bolus dose might be better than the more frequently,
Large bolus IV iron → Erythropoiesis +

Storage Iron +++

Unbound Iron

LDL Oxidation

? Accelerated atherosclerosis

Fig. 1. Effects of large bolus i.v. iron.

i.e. weekly, administered iron gluconate is premature. While infrequent administration is often convenient, what is not known is whether the larger doses required with the monthly iron sucrose might be toxic compared to the smaller doses of iron gluconate administered weekly. Recent studies from others and us have demonstrated that large rapid infusion of iron is associated with super-saturation of transferrin, leading to the possibility of highly reactive unbound iron transiently present in the circulation [2,3]. In our study [3], the most specific marker of lipid peroxidation, F2 isoprostanes measured by mass spectroscopy, increased following intravenous bolus infusion of large doses of iron (pre 199 ± 19 vs post 233 ± 25 pg/ml, P < 0.004). There was also a time-dependent increase in F2 isoprostane esterified to plasma lipoproteins that very closely correlated with plasma iron concentration. Further, larger bolus infusion, unlike smaller frequent infusion, of iron is more likely to lead to tissue iron deposition due to the persistence of high concentration of iron in the blood for longer time (Figure 1) [4,5].

While studies are required to determine whether infusion of iron more frequently but at very low doses reduces the risk of lipoprotein peroxidation and iron deposition, it is premature for Kosch et al. to conclude now that the convenience of a large monthly bolus infusion might offset its potential for exceeding transferrin binding capacity and causing lipoprotein peroxidation and iron deposition.

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3. Salahudeen AK, Oliver B, Bower JD, Roberts LJ. Increase in plasma esterified F2-isoprostanes following intravenous iron infusion in patients on haemodialysis. Kidney Int 2001; 60: 1525–1531

Reply

Sir,

In his letter Dr Salahudeen claims that high dose i.v. iron leads to enhanced lipid peroxidation. This statement is based on work the author has published in Kidney International [1]. In this paper haemodialysis patients were infused 700 mg of iron dextran over 1 h and esterified F2-isoprostanes were determined as a measure of lipid peroxidation. They found over-saturation of transferrin (165%) and an increase of F2-isoprostane from 199 pg/ml at baseline to 233 pg/ml 30 min after the 1 h infusion of iron dextran. Based on this observation they concluded that high dose iron dextran leads to transferrin over-saturation which in turn causes enhanced lipid peroxidation. For these reasons, high dose i.v. iron is detrimental to dialysis patients. The major problem with the work of Salahudeen et al. [1] is the fact that their haemodialysis patients have perfectly normal F2-isoprostane values in the range of 200 pg/ml (both at baseline and after i.v. iron dextran). This is in stark contrast to previous work by Handelman et al. [2], where haemodialysis patients were reported to have plasma values of esterified F2-isoprostane ranging from 500 to 3500 pg/ml. In light of these data the increase from 199 to 233 pg/ml seems to me more or less irrelevant. The discrepancy in F2-isoprostane values in dialysis patients may point to the fact that much is yet still unknown about the metabolism of this compound in renal failure patients (which is freely admitted in the paper of Handelman et al. [2]).

A second concern is the measurement of serum iron immediately after the infusion of high doses of iron. To quote Seligman and Schleicher [3] in their seminal paper on comparison of methods used to measure serum iron in the presence of iron gluconate or iron dextran: ‘Methods used to measure serum iron will cause in vitro dissociation of iron bound to gluconate or dextran complexes’. Thus, the observation of over-saturation of transferrin after iron administration may turn out to be a laboratory artefact. If one prefers to buy the concept of over-saturation, as Salahudeen obviously does, one should have mentioned the work of Sunder-Plassmann and Hörl [4] showing that in contrast to iron gluconate (125 mg) and iron dextran (700 mg) there is no transferrin over-saturation with the use of iron sucrose (100 mg).

This leads me to my last comment. In his letter Dr Salahudeen does not address the fact that he was using 700 mg of iron dextran, while we were using 250 mg of iron sucrose. For all fairness, we are talking here different dose and different compound, and I think this should have been addressed in the letter.

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1. Salahudeen A, Oliver B, Bower JD, Roberts LJ. Increase in plasma esterified F2-isoprostanes following intravenous iron infusion in patients on hemodialysis. Kidney Int 2001; 60: 1525–1531
3. Seligman PA, Schleicher RB. Comparison of methods used to measure serum iron in the presence of iron gluconate or iron dextran. Clin Chem 1999; 45: 898–901