Intravenous administration of iron in epoetin-treated haemodialysis patients—which drugs, which regimen?

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Introduction

There has been a plethora of literature on iron manage-ment in erythropoietin (Epo)-treated patients in recent times [1–9]. This includes published original clinical research [1–3], state-of-the-art reviews [4–7], and clin-ical guidelines generated by advisory committees on both sides of the Atlantic [8,9]. If we were to summar-ize in one statement the main message from all this literature we would conclude: 'still no reliable laborat-ory test for iron deficiency; oral iron of limited use; need for regular and frequent i.v. iron in the majority of patients on Epo'.

With all this published information, why then have the editors felt the need to commission yet another article? (The request was for 'a short and snappy piece that can be read over a cup of coffee'! E. Ritz, personal communication.) Is the message recommending the regular use of i.v. iron not now universally accepted and adopted? A recent analysis of HCFA data in the USA suggests otherwise [10], and data from the recently published European Survey on Anaemia Management (ESAM) are similarly pessimistic [11].

The aim of this article is, however, not to report the benefits of i.v. iron, nor the indications for its use, but rather to discuss the different preparations available and the various treatment regimens.

Are all i.v. iron preparations the same?

There are at least four different i.v. iron preparations available worldwide: iron dextran, iron sucrose, iron gluconate, and iron dextrin (polymaltose). All of these have very different molecular weights, physico-chemical characteristics, degradation kinetics, and side-effect profiles [12]. Even within these classes, there are differences, e.g. the two iron dextran preparations marketed in the USA (Dexferrum and INFeD) have molecular weights of 265 and 90 kDa respectively [13]. Iron sucrose is a smaller molecule (43 kDa), and there is some controversy regarding the molecular size of iron gluconate. Geisser et al. found it to be about 37 kDa [14], while Nissenson et al. reported a molecu-lar weight of 350 kDa [15].

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All the i.v. iron preparations have in common a central core containing elemental iron, shielded by a carbohydrate shell. Once injected in vivo, the iron–car-bohydrate complex is metabolized (probably in the reticulo–endothelial system), the iron is released where it then binds to transferrin in plasma, and the redundant carbohydrate moiety is then cleared via the liver. The degradation of the various iron complexes is, however, very different. In general, iron is most rapidly released from the smaller molecular weight compounds, and is released more slowly from the iron dextran preparations [12]. This property therefore determines the maximum dose that can be administered at any one time. For example, up to 1000 mg or more of iron dextran may be given as a single dose; the maximum dose of iron sucrose is 500 mg, and that of iron gluconate is 125 mg. If too much i.v. iron is given all at once, there is a danger that the iron will be released from the complex too rapidly and overload the buffering capacity of the transferrin molecule to bind it. This may result in 'free iron' reactions [16] which are anaphylactoid in nature. Although the symptoms/signs are similar, they must not be confused with the more severe and life-threatening anaphylactic reactions seen in a small proportion of patients given i.v. iron dextran [17,18]. This latter complication is peculiar to iron dextran, and is due to an immune-mediated reaction in patients who have dextran antibodies. Since there have been fatalities with iron dextran [17], and now that there are alternative iron preparations available, dextran-containing iron compounds should be used only when absolutely neces-sary. For patients who have had a previous iron dextran reaction, it is perfectly safe to give an alternative iron preparation since the allergy is specific to the dextran portion of the molecule [19].

Which i.v. iron preparation to use?

The choice of i.v. iron preparation will be influenced by various factors. First, not all preparations are available in every country (although availability is increasing all the time). Secondly, the patient popula-tion will determine which i.v. iron can be used: although it is practical to give haemodialysis patients a dose once-weekly, or even thrice-weekly during dia-lysis, such a regimen would be impossible in pre-dialysis or peritoneal dialysis patients. Thirdly, treat-ment regimens involving at least once-weekly dosing

can utilize any i.v. iron preparation; those involving once-monthly dosing are less suitable for iron gluconate due to the limitations on maximum dose. Few studies have compared the safety and efficacy of the different i.v. iron compounds, and those that have been done show little difference [20]. Iron dextran has the potential problem of anaphylactic reactions [17,18], iron gluconate may cause 'free iron' reactions [16], and although iron dextrin (polymaltose) is widely used in France and Australia it is licensed only for intramuscular use and not for i.v. administration. Iron sucrose has an excellent safety record, and mid-range doses (up to 500 mg) can be given to pre-dialysis and peritoneal dialysis patients. Doses up to 300 mg may be safely given over 2 h [21], but doses of 500 mg should be administered as an infusion over 3.5 h or longer.

Which treatment regimen to use?

There are two ways of administering i.v. iron, either as a 'push' (bolus) or as an infusion. Clearly the bolus injection has the benefit of simplicity and avoids the need for infusion pumps, bags of saline, and infusion lines. Doses of 100 mg of either iron dextran [22] or iron sucrose [23] may be given safely as a 'push'. Until further data are available, larger doses must be administered as an infusion, usually over 2–3 h.

For haemodialysis patients, there is greater flexibility with the dosing regimen. Some units use very low doses of iron (20–60 mg) given every dialysis session [24], others use doses of 100 mg given every week [23], while yet others administer doses of 200–300 mg every month [25]. Clearly the intensity of dosing will depend on the perceived iron deficit; in some cases aggressive iron administration will be required to correct absolute iron deficiency, while in other instances smaller doses may be used as maintenance iron supplementation. There is some debate about whether frequent low-dose i.v. iron administration is safer than less frequent high doses. In a retrospective analysis of claims data from Medicare dialysis patients, Collins et al. [26] found a significant relationship between the frequency of i.v. iron dosing and increased risk of death from infection. In a subsequent analysis, again using Medicare claims data, the same workers reported a significantly higher risk of infection-related death in patients who received more than 17 vials of iron during a 6-month period [27]. Banyai et al. [28] found higher levels of bleomycin-detectable free iron (BDI) in haemodialysis patients given doses of 100 mg iron sucrose, compared with those obtained after 10, 20, 40, and 50 mg. Theoretically, these higher levels of BDI could predispose the patient to reactions and infections; however, there is no evidence that this is relevant clinically.

Recently, Gupta et al. [29] reported a novel means of supplying iron to the haemodialysis patient, namely by adding soluble iron pyrophosphate to the dialysate. This mode of administration was assessed in 10 haemodialysis patients who received increasing concentrations of iron pyrophosphate up to 12 µg/dl in the

dialysate over a 6-month period. The requirements for i.v. iron were dramatically reduced in this group (10 ± 23 mg/week; 2 of 10 patients) compared with a control group continuing on i.v. iron dextran (56 ± 37 mg/week; 11 of 11 patients), and no significant adverse effects were seen [29].

For pre-dialysis and peritoneal dialysis patients, the preferred treatment regimen for i.v. iron is a larger dose given less often, e.g. once a month. This is both to reduce the inconvenience of frequent visits to hospital, and to preserve the veins for possible future vascular access. Doses of 300 mg iron sucrose infused over 2 h have proved to be a safe and effective treatment regimen [21].

Need for a test dose?

One of the greatest farces in iron management is the use of a test dose of i.v. iron sucrose or gluconate in patients receiving their first exposure to the preparation. The Drug Regulatory Authorities have demanded it; many doctors do not use it. Historically, this has dated from the recognition that iron dextran induces a low but significant incidence of anaphylactic reactions [17,18]. Thus, although a test dose is entirely appropriate for iron dextran, unfortunately this practice has been extrapolated to other (non-dextran-containing) i.v. iron preparations. The anaphylactic reaction is, however, specific for the dextran-containing iron preparations, and there is no cross-reactivity with iron sucrose or gluconate. Regrettably, the habit has stuck, and it is clearly much harder to persuade the Regulatory Authorities that a test dose is *not* required, than it would be to introduce this concept in the first place.

The use of a test dose for iron sucrose or gluconate is, however, irrational and unscientific for several reasons. First, there are no documented antibodies against sucrose or gluconate as there are for dextran. Secondly, despite over 40 years' experience with i.v. iron sucrose and gluconate, fatalities with these preparations have not been reported as they have for iron dextran. Thirdly, the likelihood of a patient developing an allergic reaction to i.v. iron sucrose or gluconate is much less than for certain other drugs such as i.v. penicillin or vancomycin, but no test dose is specified for these latter compounds. Fourthly, the lack of any reaction to a test dose does not mean the patient will not have a reaction in the future; dextran-induced anaphylaxis has been described in patients who have received several previous doses of i.v. iron dextran with no problems [30]. Finally, the practice of using a test dose can lull the doctor or nurse into a false sense of security, i.e. since the patient has been fine, the clinician feels more relaxed about using i.v. iron. As such, therefore, the use of a test dose may be more hazardous than not using it at all. A more sensible and rational approach would be to abandon the test dose for iron sucrose and gluconate, while retaining the necessary caution in all patients receiving i.v. iron,

including the need for full resuscitation facilities being available on-site. Persuading the Regulatory Authorities of this, however, may take some time, and in the meantime, test doses will continue to be used in some units and not others.

Conclusions

Intravenous iron supplementation has quite rightly grown in popularity in Epo-treated patients over the last decade. It is effective in correcting the commonest cause of a poor response to Epo, and its aggressive use can reduce Epo dose requirements [1,2]. There have, however, been few randomized controlled studies of i.v. iron in this setting, and much of our practice has been guided by anecdotal reports and personal experience.

We need more information on whether frequent low-dose administration is preferable (or harmful), and what the optimum ferritin is in patients on Epo. In addition, there is a need to investigate the maximum dose of iron that can be given safely as an i.v. bolus since, with the increasing use in pre-dialysis patients, prolonged infusions are costly and impractical. In the meantime, the most important message to get across in the light of the recent HCFA and ESAM data analyses [10,11] is the need for regular and frequent i.v. iron supplementation in patients receiving Epo; which drug and which treatment regimen are secondary considerations.

References

1. Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 1995; 26: 41–46
2. Macdougall IC, Tucker B, Thompson J, Tomson CRV, Baker LRI, Raine AEG. A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 1996; 50: 1694–1699
3. Besarab A, Amin N, Ahsan M *et al.* Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *J Am Soc Nephrol* 2000; 11: 530–538
4. Fishbane S, Maesaka JK. Iron management in end-stage renal disease. *Am J Kidney Dis* 1997; 29: 319–333
5. Macdougall IC. Strategies for iron supplementation: oral versus intravenous. *Kidney Int* 1999; 55 [Suppl 69]: S61–S66
6. Matzke GR. Intravenous iron supplementation in end-stage renal disease patients. *Am J Kidney Dis* 1999; 33: 595–597
7. Nissenson AR, Strobos J. Iron deficiency in patients with renal failure. *Kidney Int* 1999; 55 [Suppl 69]: S18–S21
8. NKF-DOQI Work Group. NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. *Am J Kidney Dis* 1997; 30 [Suppl 3]: S192–S240
9. European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 1999; 14 [Suppl 5]: 1–50
10. Frankenfield D, Johnson CA, Wish JB, Rocco MV, Madore F, Owen WF. Anemia management of adult hemodialysis patients in the US: results from the 1997 ESRD Core Indicators Project. *Kidney Int* 2000; 57: 578–589
11. European Survey on Anaemia Management. *Nephrol Dial Transplant* 2000; 15 [Suppl 4]: 1–76
12. Macdougall IC, Chandler G, Armstrong A, Breen C, Harchowal J, Cavill I. Characterisation of iron availability from three different IV iron preparations in dialysis patients. *J Am Soc Nephrol* 1997; 8: 221
13. Lange R, Diamant M, Marx JJM. Parenteral administration of iron: possibilities and risks. *Pharm Weekbl* 1997; 132: 103–111
14. Geisser P, Baer M, Schaub E. Structure/histotoxicity relationship of parenteral iron preparations. *Arzneimittel Forschung* 1992; 42: 1439–1452
15. Nissenson AR, Lindsay RM, Swan S, Seligman P, Strobos J. Sodium ferric gluconate complex in sucrose is safe and effective in hemodialysis patients: North American Clinical Trial. *Am J Kidney Dis* 1999; 33: 471–482
16. Zanen AL, Adriaansen HJ, van Bommel EFH, Posthuma R, de Jong GMT. 'Oversaturation' of transferrin after intravenous ferric gluconate (Ferrlecit) in haemodialysis patients. *Nephrol Dial Transplant* 1996; 11: 820–824
17. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. *J Am Med Assoc* 1980; 243: 1726–1731
18. Fishbane S, Ungureanu VD, Maesaka JK, Kaupke CJ, Lim V, Wish J. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; 28: 529–534
19. Levin N, Cavallo G, Spinowitz B, Adhikarla R, Gagnon S, Charytan C, Van Wyck D. Safety of iron sucrose injection for iron deficiency in patients with anaphylaxis after iron dextran: preliminary results. *J Am Soc Nephrol* 1999; 10: 80A
20. Schaefer RM, Bettger H, Teschner M, Bahner U. A randomised, controlled parallel-group study for comparison of iron sucrose (Venofer) *vs* iron gluconate (Ferrlecit) in haemodialysis patients treated with epoetin. *Kidney Blood Pressure Res* 1999; 22: 238
21. Chandler G, Harchowal J, Macdougall IC. Intravenous iron hydroxysaccharate: establishing the optimum dose. *J Am Soc Nephrol* 1997; 8: 217
22. St. Peter WL, Lambrecht LJ, Macres M. Randomized crossover study of adverse reactions and cost implications of intravenous push compared with infusion of iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; 28: 523–528
23. Macdougall IC, Chandler G, Elston O, Harchowal J. Beneficial effects of adopting an aggressive intravenous iron policy in a hemodialysis unit. *Am J Kidney Dis* 1999; 34 [Suppl 2]: S40–S46
24. Sunder-Plassmann G, Hörl WH. Importance of iron supply for erythropoietin therapy. *Nephrol Dial Transplant* 1995; 10: 2070–2076
25. Silverberg DS, Iaina A, Peer G, Kaplan E, Levi B, Frank N, Steinbruch S, Blum M. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Am J Kidney Dis* 1996; 27: 234–238
26. Collins A, Ebben J, Ma J. Frequent IV iron dosing is associated with higher infectious deaths. *J Am Soc Nephrol* 1997; 8: 190A
27. Collins A, Ebben J, Ma J, Xia H. IV iron dosing patterns and mortality. *J Am Soc Nephrol* 1998; 9: 204A
28. Banyai S, Rainer V, Derfler K, Druml W, Horl WH, Sunder-Plassmann G. Bleomycin detectable free iron (BDI) is present in patients on intravenous iron therapy. *J Am Soc Nephrol* 1998; 9: 198A
29. Gupta A, Amin NB, Besarab A, Vogel SE, Divine GW, Yee J, Anandan JV. Dialysate iron therapy: infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis. *Kidney Int* 1999; 55: 1891–1898
30. Jayakumar S, Jayakumar SA. Iron dextran anaphylactic-like reaction after a negative test dose and subsequent successful administration of three doses. *Dial Transplant* 2000; 29: 198–201