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Strategies for iron supplementation: Oral versus intravenous

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Strategies for iron supplementation: Oral versus intravenous. Iron supplementation has become an integral part of the management of patients receiving epoetin therapy, and clinicians have found it necessary to learn how and when to use it to the best advantage. Three routes of administration for iron are available: oral, intramuscular, and intravenous. Oral iron has the advantage of being simple and cheap, but it is limited by side-effects, poor compliance, poor absorption, and low efficacy. Intravenous iron is the best means of guaranteeing delivery of readily available iron to the bone marrow, but it requires greater clinical supervision. The i.v. iron preparations vary widely in their degradation kinetics, bioavailability, side-effect profiles, and maximum dose for single administration. Iron dextran is hampered by a small but significant risk of anaphylaxis, whereas all i.v. iron preparations can induce "free iron" reactions if the circulating plasma transferrin is overloaded. Intravenous iron may be given in advance of epoetin therapy, as concomitant treatment to prevent the development of iron deficiency, as treatment of absolute or functional iron deficiency, or as adjuvant therapy to enhance the response to epoetin in iron-replete patients. Markers of iron status that may indicate a need for i.v. iron include a serum ferritin of less than 100 μg/liter, a transferrin saturation of less than 20%, and a percentage of hypochromic red cells more than 10%. Various regimens are available for giving i.v. iron: low-dose administration of 20 to 60 mg every dialysis session in hemodialysis patients, medium-dose administration of 100 to 400 mg, and high-dose administration of 500 to 1000 mg. Iron sodium gluconate can only be given as a low-dose regimen because of toxicity, whereas the only preparation suitable for high-dose administration is iron dextran. Although concerns have been raised regarding iron overload and long-term toxicity with i.v. iron therapy in terms of increased risk of infections, cardiovascular disease, and malignancy, there is little evidence to substantiate this in patients receiving epoetin. Care should be taken, however, to prevent the serum ferritin rising above 800 to 1000 μg/liter and the transferrin saturation above 50%. Provided this is done, the benefits of i.v. iron almost certainly outweigh the risks in terms of optimizing the response to epoetin therapy.

When epoetin therapy was first introduced into clinical practice 10 years ago, the development of functional iron deficiency and the need for iron supplementation were scarcely anticipated. It has since become very apparent that an inadequate iron supply to the bone marrow is the most common cause of an impaired response to epoetin, and that iron supplementation is frequently required, possibly in up to 90% of patients treated [1]. Nephrologists have found it necessary to understand the complexities of iron metabolism, to differentiate between absolute and functional iron deficiency, to recognize the value of the various tests of iron status, and to develop strategies for giving patients supplemental iron therapy [2]. The latter can be given in several different clinical situations: (*a*) as an alternative to epoetin therapy with the aim of achieving a modest rise in hemoglobin, particularly when economic constraints limit the use of epoetin; (*b*) prior to epoetin therapy to boost the iron stores prophylactically; (*c*) as a treatment for absolute or functional iron deficiency developing in patients receiving epoetin; and (*d*) as an adjuvant therapy to enhance the response to epoetin even in iron-replete patients.

The aim of this article is to discuss the various regimens available for supplementing iron in patients with renal anemia. Three routes of administration are available: oral, intramuscular, and intravenous. The first two have severe limitations, particularly in the context of patients receiving epoetin therapy, and the intravenous route is increasingly used in such patients.

ORAL IRON

Several iron salts are available in tablet or liquid form for oral ingestion, as listed in Table 1. All of these are fairly simple and cheap, but usually two or three doses are required daily. Despite claims by some manufacturers to the contrary, there is little advantage in the use of any one oral preparation over any other. Ferrous sulfate, which supplies 65 mg of elemental iron per 200 mg tablet, is the most widely used oral iron preparation.

The main drawbacks with oral iron are side-effects, poor compliance, and limited absorption from the gut. Gastrointestinal intolerance with oral iron therapy is dose related and common (up to 20% of patients), and this frequently leads to poor compliance [3]. Tolerance can be improved by ingesting the iron tablets along with food, but this is associated with a corresponding decrease

Key words: epoetin therapy, transferrin, anaphylaxis, hypochromic red cells, bone marrow, renal anemia.

Table 1. Available oral and parenteral iron preparations[a]

Oral preparations	Intravenous preparations	Intramuscular preparations
Ferrous sulfate	Iron dextran[c]	Iron sorbitol citrate
Ferrous fumarate	Iron dextrin[c]	
Ferrous gluconate	Iron hydroxysaccharate	
Ferrous succinate	Iron sodium gluconate	
Iron polymaltose[b]		
Polysaccharide-iron complex		

[a] This list is not exhaustive; other oral and parenteral iron preparations may be available
[b] Can also be administered parenterally (intravenous or intramuscular injection)
[c] Can also be administered by intramuscular injection

in iron absorption. Furthermore, if functional iron deficiency develops in patients receiving epoetin who have a serum ferritin above 100 μg/liter, then gastrointestinal absorption of iron will also be severely impaired [4].

All of these factors limit the usefulness of oral iron supplementation in patients on epoetin, and administration of adequate amounts of iron orally is often impossible. This is because the demands for iron during epoetin treatment frequently exceed the maximum quantity that can be supplied via the oral route. Indeed, comparative studies of oral and i.v. iron have shown that only the latter is capable of providing an adequate supply of iron during epoetin treatment [5–8]. In such situations, the use of parenteral iron preparations becomes a necessity in order to optimize the therapeutic response to epoetin.

INTRAMUSCULAR IRON

This route is little used in patients receiving epoetin, although there are a few centers that supplement iron intramuscularly. Several preparations are available for intramuscular administration (Table 1) and, as for oral iron, there is little evidence to suggest that any one compound is better than any other. There are several disadvantages of the intramuscular route. First, the injections are painful and can leave a brownish discoloration on the skin that can persist for several weeks. Second, there is a risk of bleeding into the muscle, which is exacerbated by uremic platelet dysfunction in renal patients. Third, there are reports of muscle sarcomas developing at the site of injection, and finally, the absorption and bioavailability from this route can be highly variable. Few studies have examined in any detail the use of intramuscular iron in patients receiving epoetin therapy.

INTRAVENOUS IRON

The use of i.v. iron has increased dramatically over the last five years. Several i.v. iron preparations are available worldwide (Table 1), although each country may have access to only one or two of them. For example, at the time of writing this article, the only licensed iron compound in the United States is iron dextran (two different formulations). In the United Kingdom, the only iron preparation with a product license is iron hydroxysaccharate (Venofer). In France, iron dextrin (polymaltose), iron hydroxysaccharate, and iron sodium gluconate are all available. In Germany, both iron hydroxysaccharate and iron sodium gluconate are used, and in Australia, both iron dextrin and iron hydroxysaccharate are available.

These different iron preparations vary greatly in their molecular size, their degradation kinetics (how rapidly iron is released from the complex), their bioavailability, and their side-effect profiles. In general, the smaller the complex, the more rapidly iron is released to bind to transferrin and to supply the marrow [9].

The concern with lower molecular weight complexes such as iron sodium gluconate is that iron may be released too rapidly and may overload the ability of transferrin to bind it, leading to free iron reactions [10]. Thus, lower doses of this iron preparation must be used (62.5 to 125 mg) compared with, for example, iron dextran, 1000 mg of which may be given safely. A randomized prospective study compared 200 mg of i.v. iron dextran, iron dextrin, and iron hydroxysaccharate and found that iron was released onto transferrin more rapidly with iron hydroxysaccharate compared with the other two preparations, and that the increases in serum ferritin were least marked with iron dextran [9]. A comparison of different dosages of iron hydroxysaccharate given intravenously over two hours suggested that doses of 200 mg or 300 mg could be administered safely, but that "free iron" reactions were observed when doses of 400 mg (incidence 6%) and 500 mg (incidence 36%) were given [11].

The other major adverse effect, which is exclusively seen with iron dextran, is anaphylaxis, which may be life-threatening (see below). For this reason, a test dose is strongly advised before administering a full treatment dose of this preparation.

WHEN TO USE INTRAVENOUS IRON

Nephrologists vary widely in their usage of i.v. iron in dialysis patients, with some adopting fairly aggressive protocols aiming to keep the serum ferritin above 200 μg/liter and others using it only when all else fails. Although all markers of iron status have their limitations, it is reasonable to consider using i.v. iron if the serum ferritin is less than 100 μg/liter, the transferrin saturation is less than 20%, or the percentage of hypochromic red cells is more than 10%. Administering i.v. iron to iron-deficient patients will often induce a mild to moderate increase in hemoglobin concentration by 1 to 2 g/dl even in the absence of epoetin, and indeed, this practice was

Table 2. Studies of aggressive i.v. iron supplementation in patients receiving EPO

Reference	No. of patients	Iron preparation	EPO dose reduction
Schaefer & Schaefer (1992) [16]	14	gluconate	47%
Nyvad et al (1994) [17]	34	sucrose	27%
Al-Momen et al (1994) [18]	109	sucrose	—
Sunder-Plassmann & Hörl (1995) [19]	64	sucrose	70%
Fishbane et al (1995) [20]	52	dextran	46%
Macdougall et al (1996) [22]	37	dextran	19%
Silverberg et al (1996) [23]	41	sucrose	61%
Sepandj et al (1996) [24]	50	dextran	35%
Taylor et al (1996) [25]	46	gluconate	33%
Ahsan et al (1996) [26]	7	dextran	26%

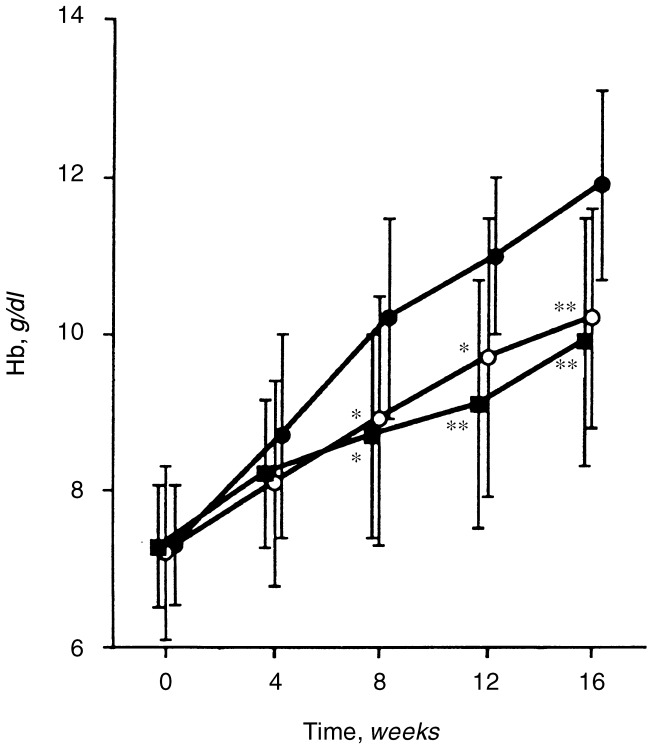

Fig. 1. Hemoglobin response (mean ± SD) in three groups of erythropoietin-treated patients with different regimens of iron supplementation. Symbols are: (●) i.v. iron; (○) oral iron; (■) no iron; $*P < 0.05$; $**P < 0.005$ vs. i.v. iron-treated group. Taken from Macdougall et al [22]; used with permission.

adopted by some clinicians long before the advent of epoetin [12, 13]. Even today, there are those who believe that the maximum gain should be obtained from i.v. iron before the more costly epoetin therapy is instituted [14].

The second clinical situation in which i.v. iron is used is in preparation for epoetin therapy where the iron stores, as judged by the serum ferritin, are likely to be inadequate to support a rise in hemoglobin concentration of 4 to 5 g/dl. Previous work suggested that a serum ferritin of 20 μg/liter was required for every 1 g/dl of hemoglobin [15]. Thus, patients due to start epoetin therapy with a ferritin of less than 100 μg/liter are highly likely to develop iron deficiency, and in such patients, it is advisable to start i.v. iron concomitantly.

The third scenario when i.v. iron is given is when a patient on epoetin develops either absolute or functional iron deficiency. Absolute iron deficiency is easier to diagnose and is present when the serum ferritin falls below 50 μg/liter in dialysis patients. Functional iron deficiency is harder to recognize; the serum ferritin is normal or high, and the problem is with adequate amounts of available iron being delivered to the marrow. This is usually manifest by a transferrin saturation value of less than 20% or a hypochromic red cell measurement of more than 10%. Oral iron is useless in this condition because very low levels are absorbed [4], and i.v. iron is mandatory to optimize the response to epoetin and to prevent wastage of this costly drug.

The final clinical context that has received a lot of attention in recent years is the aggressive use of i.v. iron supplementation to enhance the response to epoetin, even in patients who are iron replete [16–27]. The rationale for this is that iron supply to the erythron is a rate-limiting step in the process of erythropoiesis and that this can be overcome by administering iron in a readily available form intravenously. Some of the studies that have supported the development of this practice are listed in Table 2, and reductions in epoetin dosage have varied widely from 19% to 70%. Part of the reason for this wide variability is that some of the studies included patients with absolute iron deficiency when one would expect i.v. iron to be even more effective. Several studies, however, examined only iron-replete patients, and two in particular were conducted as randomized prospective controlled trials, with an oral iron control arm. Macdougall et al randomized 37 iron-replete (ferritin of more than 100 μg/liter) patients to receive either i.v. iron dextran ($N = 13$), oral iron (ferrous sulfate 200 mg tds; $N = 12$), or no iron supplementation ($N = 12$) during the correction phase of epoetin therapy [22]. The group of patients treated with regular i.v. iron had the best hemoglobin response, maintained their serum ferritin at pretreatment levels, and had the lowest dose requirements of epoetin (Fig. 1). Similarly, in a study by Fishbane et al, 52 dialysis patients in the correction phase of epoetin therapy who had ferritin levels of more than 100 μg/liter were randomized to receive either i.v. iron dextran ($N = 32$) or oral iron ($N = 20$) [20]. Again, the hematocrit level increased significantly in the i.v. iron group compared with the oral iron group, and substantial reductions in epoetin dose requirements were seen (Fig. 2). There seems little doubt, therefore, that in order to maximize the response to epoetin therapy, i.v. iron will be required in a substantial number of patients.

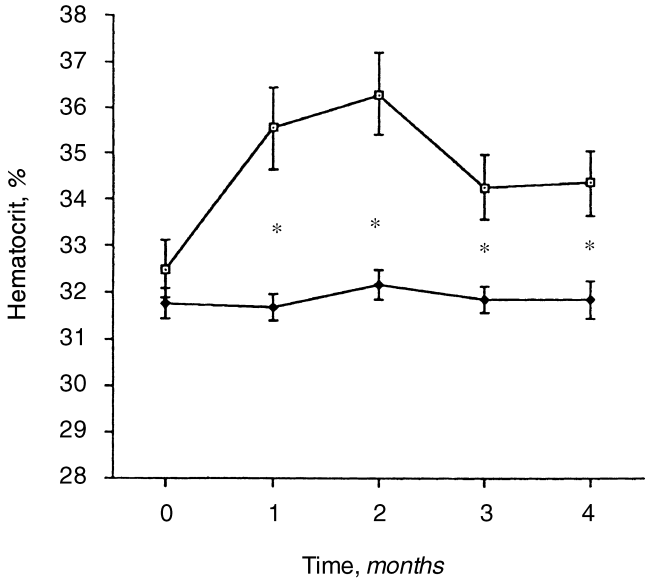

Fig. 2. Mean hematocrit in two groups of patients receiving erythropoietin. Squares indicate the intravenous iron group; diamonds indicate the oral iron group. *$P < 0.05$. Taken from Fishbane et al [20]; used with permission.

Table 3. Regimens for administering i.v. iron

"Low dose"	20–60 mg every dialysis session • hemodialysis patients only • any of iron preparations suitable • may be given as i.v. "push"
"Medium dose"	100–400 mg • usually i.v. infusion; lower doses may be given as slow bolus injection • all iron preparations (maximum dose of iron sodium gluconate = 62.5–125mg)
"High dose"	500–1000 mg • must be given as i.v. infusion • only iron dextran suitable • suitable as a top-up for patients with large iron deficit

POSSIBLE REGIMENS FOR ADMINISTERING INTRAVENOUS IRON

Apart from the kinetic bioavailability study mentioned earlier [9], there are no randomized controlled prospective studies comparing one i.v. iron preparation with another. It seems likely, however, that there will be little to distinguish them in terms of efficacy, and that what matters most is the recognition that many patients on epoetin will require i.v. iron supplementation in one form or another.

The two most important factors determining which i.v. iron regimen will be used are (*a*) modality of renal replacement therapy and (*b*) what iron preparations are available in the particular country of origin. For example, with hemodialysis patients, it is practical to give doses of 20 to 60 mg three times a week during each dialysis session. This is not the case with continuous ambulatory peritoneal dialysis (CAPD) or predialysis patients, who would far prefer to receive a larger dose of 200 to 500 mg once a month. At the time of writing this article, iron dextran is the only preparation available in the United States (although this is changing), and thus, this clearly limits the choice of i.v. iron regimen in this country.

It is perhaps convenient to consider the various strategies available as "low-dose," "medium-dose," and "high-dose" i.v. iron (Table 3). Iron sodium gluconate is useful for only low-dose administration because its toxicity limits the dose to a maximum single administration of 62.5 to 125 mg. Iron hydroxysaccharate, iron dextrin, or iron dextran may also be used for this purpose, and all of these agents may be given as an i.v. "push" [28]. Medium-dose administration of 100 to 400 mg may be provided by either iron hydroxysaccharate, iron dextrin, or iron dextran, and is practical for once-weekly or once-fortnightly administration. Again, a single dose of 100 mg can be given as a slow i.v. injection, whereas doses of 200 mg or more should be given as an i.v. infusion. High-dose i.v. iron supplementation is less popular than before because side-effects such as arthralgia, myalgia, and other aches and pains are more common at this dose. The only i.v. iron preparation that can be given as a single dose of 500 to 1000 mg is iron dextran, which must be administered as a slow infusion over several hours. This dose would, however, be practical for a patient who lives a considerable distance from hospital or who is unwilling to attend more than once every three to four months.

MONITORING INTRAVENOUS IRON SUPPLEMENTATION

Patients receiving regular i.v. iron should be monitored closely for clinical or laboratory evidence of iron toxicity or overload. Abnormal liver function tests, a serum ferritin greater than 800 to 1000 μg/liter, or a transferrin saturation greater than 50% may all indicate iron overload and increase the risk of parenchymal deposition of iron in the liver, pancreas, and heart. The aim should be, therefore, to monitor these parameters regularly and stop i.v. iron if these levels are exceeded. Serum ferritin and transferrin saturation should be measured at least one week after administration of i.v. iron for modest doses (100 to 200 mg) [9] and at least two weeks after i.v. iron for larger doses, in order to exclude a spuriously high measurement.

REACTIONS TO INTRAVENOUS IRON

There appear to be two types of reaction to i.v. iron. The first is a type I IgE-mediated anaphylactic reaction,

which is seen exclusively to iron dextran and is due to preformed dextran antibodies. The reported incidence of anaphylaxis to iron dextran is approximately 0.7% [29].

The second reaction is anaphylactoid in nature, causing one or more symptoms such as breathlessness, wheezing, arthralgia, myalgia, abdominal or back pain, nausea, vomiting, and hypotension. This is probably due to transient overload of the transferrin molecule, resulting in small amounts of free iron in circulation [10]. It is possibly histamine mediated, but it is not clear whether or not this is triggered by an immune reaction. In contrast to the iron dextran-induced anaphylaxis, the "free iron" reactions would appear to be dose-related, and it is possible to rechallenge the patient at a lower dose.

LONG-TERM TOXICITY OF INTRAVENOUS IRON

Concerns have been raised about potential iron overload and long-term toxicity with i.v. iron therapy. Although some authors have proposed that increased body iron may increase the risk of cardiovascular disease [30], this hypothesis was not supported by the findings of a recent study [31]. There are also epidemiological data to support a link between increased body iron stores and an increased risk of cancer [32], and a further study suggested that patients with iron overload had an increased risk of infection [33]. Whether these concerns are relevant in patients receiving epoetin has not been established. In some studies, for example, the serum ferritin did not change despite regular administration of i.v. iron, suggesting that all of the iron was used up in the process of erythropoiesis [22]. Because the benefits of i.v. iron can be considerable, it would appear that it is reasonable to adopt a liberal but cautious approach to this therapy, with careful monitoring of serum ferritin and transferrin saturation as indicated above.

CONCLUSIONS

Iron therapy may be given by the oral, intramuscular, and intravenous routes, but in patients receiving epoetin, the limitations of oral and intramuscular administration should be recognized. The intravenous route provides iron in a rapidly available form for erythropoiesis and bypasses some of the problems seen with oral or intramuscular iron. In hemodialysis patients, it is practical to give low-dose i.v. iron (20 to 60 mg) during each dialysis session or 100 to 200 mg once weekly, whereas in CAPD and predialysis patients, it is more sensible to give doses in the region of 200 to 500 mg every month or so. The indications for i.v. iron are varied, as is current practice among individual clinicians, but it is increasingly recognized that an aggressive policy of using i.v. iron can optimize the benefits of epoetin therapy and can result in dosage (and hence cost) reductions.

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