

*Editorial Article*

## **Nutrition, Anaemia and Erythropoietin Therapy**

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### **Introduction**

During the last decade, recombinant human erythropoietin has revolutionised the management of renal anaemia. It is highly effective in the vast majority of patients treated, causing enhanced erythropoiesis and a rise in haemoglobin concentration. This has resulted not only in amelioration of uraemic symptoms, but there has also been objective evidence of improved quality-of-life, exercise capacity, and cardiac function [1]. The most striking benefits seen have been progression of left ventricular hypertrophy which is known to account for much of the high cardiovascular morbidity and mortality seen in dialysis patients, and thus the arguments for correcting renal anaemia is now overwhelming. There is also an improvement in nutrition following erythropoietin therapy, over and above the improvement in appetite associated with correction of the anaemia.

Although erythropoietin is pivotal in stimulating erythropoiesis in patients with renal failure, it is recognised that a number of other factors are involved in this process. These include other growth factors and cytokines such as stem cell factor (SCF), interleukin-3 (IL-3), interleukin-10 (IL-10), and insulin-like growth factor-1 (IGF-1), as well as a large number of nutritional "ingredients" such as iron, folic acid, vitamin B 12, vitamin B6 (pyridoxine), ascorbic acid, thyroxine, and several trace minerals.

Poor nutrition may therefore lead to a deficiency of one or more of these factors, causing in turn a sub-optimal response to erythropoietin therapy. There has also been much discussion over the last few years as to whether it is possible to augment the response to erythropoietin with other adjuvant therapies.

The first adjuvant therapy to be recognised as being able to enhance the response to erythropoietin was intravenous iron [2,3]. Initially this was used when patients developed either absolute or functional iron deficiency, but it was subsequently found that IV iron had benefits even in iron-replete patients [4,5]. Other adjuvant therapies have since been examined (table 1), and the aim of this article is to review the evidence and potential role for these agents in the context of erythropoietin therapy.

**Table 1.** Metabolic adjuvants to epoetin therapy.

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IV iron
Folic acid
Vitamin B12
Vitamin B6
Ascorbic acid
Vitamin D
L-carnitine
Androgens
IGF-1 / IL-3

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In considering adjuvant treatment, it is important to distinguish between replacing a deficient substance and administering a surfeit of a given substance. Thus, it would appear that administration of intravenous iron has positive effects in both iron deficiency and in iron-replete states, whereas vitamin B 12 supplementation will only have a positive effect if this vitamin is deficient. In other adjuvant therapies such as carnitine, it is not clear whether the positive effects are seen in carnitine-deficient patients, carnitine-replete patients, or both.

### **IV iron**

Ever since the earliest clinical studies of erythropoietin therapy, it was observed that certain patients showing a poor response to treatment could have this reversed with IV iron administration [2,3]. Indeed, over the last decade it has become apparent that oral iron is largely

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ineffective in this context. In both absolute iron deficiency (when total body iron stores are exhausted) and functional iron deficiency (when total body iron stores are adequate but there is a failure to release the iron rapidly enough), IV iron has proved superior to oral iron, and there are various reasons for this including poor absorption, poor bioavailability, poor compliance, and the excessive demands for iron by the bone marrow during active erythropoiesis. Intravenous administration of iron, however, results

in a readily available supply of iron, which can be utilised almost immediately by the marrow [6]. More recently, it has become apparent that intravenous iron can enhance the response to erythropoietin even in iron-replete patients. Several studies have shown an augmented haemoglobin response and, perhaps more importantly, significant reductions in the dosage requirements of erythropoietin (table 2) [4,5,7,8,9,10,11,12].

**Table 2.** Studies of aggressive IV iron supplementation in patients receiving epoetin.

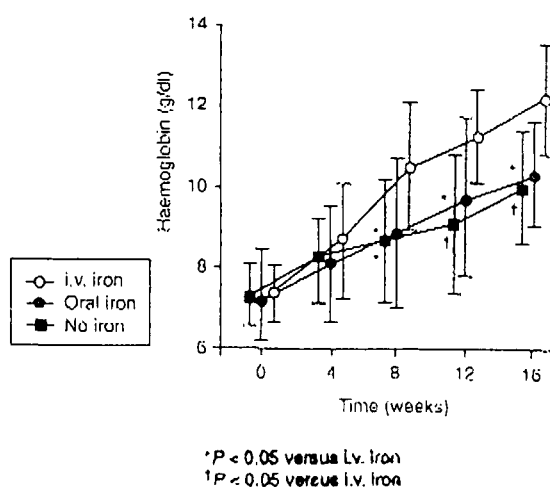
Reference	No of patients	Iron preparation	% reduction in EPO dose
Schaefer and Schaefer (1992) <sup>7</sup>	14	Gluconate	47%
Nyvad et al (1994) <sup>8</sup>	34	Sucrose	27%
Al-Momen et al (1994)	109	Sucrose	-
Sunder-Plassmann & Hbrl (1995) <sup>9</sup>	64	Sucrose	70%
Fishbane et al (1995) <sup>5</sup>	52	Dextran	46%
Macdougall et al (1996) <sup>4</sup>	37	Dextran	19%
Silverberg et al (1996) <sup>10</sup>	41	Sucrose	61%
Sepandj et al (1996) <sup>11</sup>	50	Dextran	35%
Taylor et al (1996) <sup>12</sup>	46	Gluconate	33%
Ahsan et al (1996)	7	Dextran	26

**Table 3.** Role of adjuvant treatment in patients receiving epoetin.

	Deficiency	Replete	References
IV iron	\	\	Numerous
Folic acid	\	\ (1MCV)	Pronai et al (1995) <sup>15</sup>
Vitamin B 12	\	X	Zachee et al (1992) <sup>16</sup>
Vitamin B6	\	X	Mydlik et al (1997) <sup>17</sup>
Ascorbic acid	\	\	Tarnig et al (1998) <sup>20</sup>
Vitamin D	X	\	Albitar et al (1997) <sup>24</sup>
L- carnitine	\	\	Labonia et al (1995) <sup>28</sup>
Androgens	\	X	Ballal et al (1991) <sup>31</sup>
IGF-1/IL-3	-	\	Brox et al (1996) <sup>35</sup> , Macdougall et al (1995) <sup>19</sup>
	X	\	

Two of these are randomised prospective controlled studies, one in the correction phase of erythropoietin therapy, and the other in the maintenance phase.

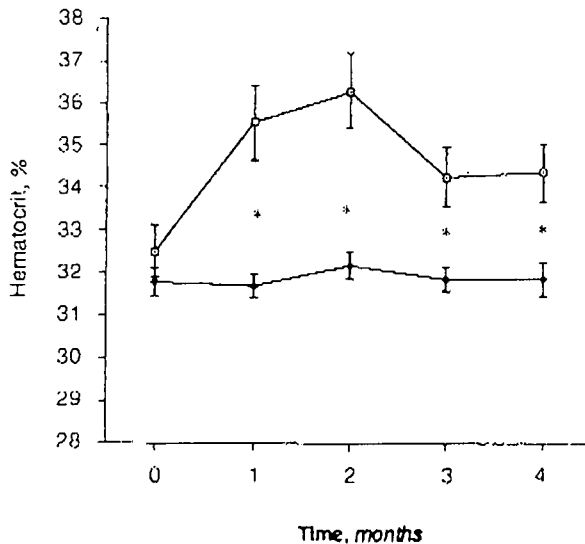
In the study by Macdougall et al [4], 37 patients were randomised to receive either intravenous iron dextran (250mg every two weeks), oral ferrous sulphate 200mg tds, or no iron supplementation. All patients had to have a serum ferritin greater than 100 p.g/l to be entered into this study. The patients in the IV iron group had the best haemoglobin response (Fig. 1), maintained their serum ferritin at baseline levels, and had the lowest erythropoietin dose requirements. In a similar study by Fishbane et al [5], patients in the maintenance phase of erythropoietin therapy were randomised to IV iron dextran (100mg every two weeks) or oral iron (ferrous sulphate or iron polymaltose).



**Fig. 1.** Haemoglobin response to i.v. iron (iron dextran 250 mg every two weeks), oral iron (ferrous sulphate 200 mg t.d.s.), or no iron in 37 patients treated with r-HuEPO[22].

There was a significant increase in haematocrit in the group of patients receiving IV iron, with no change in the oral iron group (Fig. 2). The dosage requirements of epoetin fell dramatically after two months' treatment with IV iron.

Thus, the benefits of IV iron supplementation are well-established in both iron-deficient and iron-replete states.



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

### Folic acid

Folic acid is a low molecular weight substance which is water-soluble. Folate deficiency in dialysis patients is much less common than iron deficiency, but nevertheless a number of factors make such patients prone to this condition. These include losses of folate during dialysis (especially high-flux haemodialysis), poor dietary intake of folic acid due to anorexia, and occasionally the use of drugs that interfere with folate metabolism.

Some dialysis centres advocate the regular use of folic acid supplementation in their patients, driven perhaps by the conclusions of a fairly old publication from over 30 years ago [13].

However, there is probably less dietary restriction of folate nowadays compared to the early days of dialysis, and the need for routine supplementation has been questioned [14]. It is reasonable to assume, however, that folic acid requirements will be increased in patients treated with epoetin, and hence in some patients a folate deficiency may be precipitated. Pronai et al [15] reported some resistance to epoetin in haemodialysis patients due to folate, and a clue in this study was the presence of a raised MCV. These patients responded to folic acid

supplementation at a dose of 10mg per day, despite having normal plasma levels of folic acid. Generally, measurements of red cell folate are preferable to serum folate in terms of sensitivity and specificity.

### Vitamin B12

Vitamin B12 is also a small molecular weight substance which can be lost during dialysis. Nevertheless, B12 deficiency is even less common than folate deficiency, and there is only one case report in the literature of epoetin resistance due to B12 deficiency which was corrected by giving B12 supplementation [16]. The authors then proceeded to screen the remainder of their dialysis population receiving epoetin, and in none of the 30 patients tested was a deficiency of B12 found. Thus, although it is important to include this as a cause of epoetin resistance, particularly if there is an unexplained macrocytosis, there is no indication for routine B12 supplementation in patients on epoetin.

### Vitamin B6

Vitamin B6 has a role in haem synthesis and in the incorporation of iron into haem. It is less important as a co-factor in erythropoiesis. Vitamin B6 deficiency may occur in dialysis patients as a result of poor dietary intake, impaired metabolism of the active form (pyridoxyl-5-pyrophosphate), losses in the urine (particularly when frusemide is given), and losses in the dialysate. As with iron and folate, it is likely that vitamin B6 requirements will be increased in patients receiving epoetin therapy, and this may therefore precipitate a B6-deficient state. Indeed, Mydlik et al [17] recently reported resistance to epoetin due to B6 deficiency, which was corrected by giving B6 supplementation. This may be given at a dose of 100-150mg per week, and it is also important to realise that a deficiency of vitamin B6 can occur in the red cells despite normal plasma levels of this vitamin [17].

### Ascorbic acid

A number of dialysis patients are known to develop vitamin C deficiency, and some authors have advocated routine supplementation in this patient group [18]. Nevertheless, epoetin resistance due to vitamin C deficiency has not been a problem, and the main interest with this vitamin is whether it could have a potential role in treating functional iron deficiency in patients with iron overload.

This was first suggested by Gastaldello et al [19] who treated 4 haemodialysis patients, all of whom were receiving epoetin and who had a functional iron deficiency despite the presence of iron overload. Administration of intravenous ascorbic acid improved the response to epoetin dramatically, and the effect was lost when the vitamin C was withdrawn (Fig. 3).

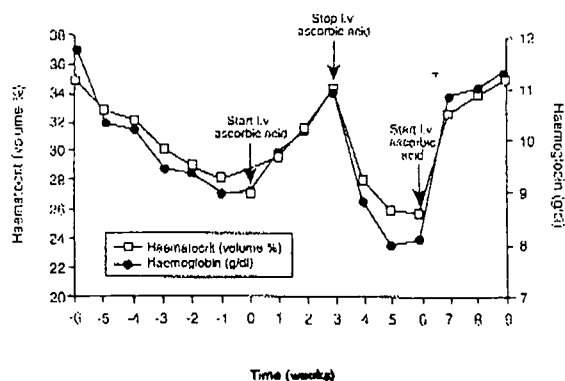


Fig. 3. Response to i.v. ascorbic acid in an iron-overloaded patient receiving r-HuEPO [27].

The response, however, was regained with further administration of vitamin C. These observations were put to the test in a randomised controlled prospective study from Taiwan [20]. Tarng et al recruited 50 haemodialysis patients with functional iron deficiency on epoetin despite high serum ferritin levels, and they were randomised to two protocols, each with a control group. The first protocol consisted of intravenous iron sucrose, 100mg across each dialysis for a total of 5 treatments. The second protocol involved administering intravenous ascorbic acid 100mg across dialysis thrice weekly for a total of 8 weeks. The patients receiving intravenous iron showed no response, but those given intravenous ascorbic acid showed a significant rise in haematocrit and a reduction in epoetin dose requirements [20]. The serum ferritin levels in these patients showed a progressive fall, the transferrin saturation levels rose, and there was a decrease in the levels of zinc protoporphyrin. The suggested explanation for this effect was mobilisation of iron from inert tissue stores, or increased iron utilisation in the erythron. Patients who may be suitable for a trial of intravenous ascorbic acid would be those who are showing a poor response to epoetin therapy despite serum ferritin levels greater than 500µg/l. Caution, however, should be observed since it is not known what the effect of this treatment strategy is on plasma oxalate levels (which should be monitored) or oxidative stress.

### Vitamin D

It has been recognised for quite some time that secondary hyperparathyroidism can exacerbate the anaemia associated with renal failure. Various explanations for this have been offered including a direct effect of PTH on erythroid progenitor cell growth, and the development of bone marrow fibrosis. More recently, this condition has also been found to be a cause of erythropoietin resistance [21] and again this seems to correlate with the degree of bone marrow fibrosis. Treatment of hyperparathyroidism by either high-dose vitamin D

or parathyroidectomy has been shown to improve renal anaemia even in patients not receiving epoetin [22,23]. Again, this has been attributed to removal of bone marrow suppression by PTH, increases in serum erythropoietin levels, and retardation of bone marrow fibrosis.

More recently, it has been found that high-dose one alfacalcidol can augment the response to epoetin, allowing reductions in dosage requirements. Two such studies have been reported within the last couple of years [24,25]. In the study by Albitar et al [24], 12 haemodialysis patients were given high-dose pulsed IV alfacalcidol, and the mean haemoglobin increased from  $8.7 \pm 1.2$  g/dl at baseline to  $10.3 \pm 0.98$  g/dl at 3 months. Goicoechea et al [25] recently published the results of a study in 28 haemodialysis patients, 21 of whom were receiving epoetin. The patients were treated with  $2\mu$ g of calcitriol intravenously after each dialysis, with subsequent dose adjustments according to PTH, calcium, and phosphate levels. After 12 months of treatment, 19 patients had shown a significant response with an increase in mean haemoglobin from  $10.6 \pm 1.5$  g/dl to  $12.2 \pm 1.5$  g/dl ( $p < 0.001$ ). The increase in haematocrit in this study correlated with the decrease in PTH levels, and it was therefore impossible to dissociate a direct effect of vitamin D from the suppression of hyperparathyroidism [25]. It is known, however, that erythroid progenitor cells in the bone marrow do possess vitamin D receptors, and it may be that calcitriol can stimulate the proliferation and differentiation of such cells. This is certainly an interesting area of research that merits further study.

### L-carnitine

Carnitine is a highly water-soluble, low molecular weight, quaternary ammonium compound which again can be lost across dialysis. It is an important carrier molecule for transporting long-chain fatty acids across the inner mitochondrial membrane, and it also appears to be important for membrane phospholipid metabolism.

Its main physiological role is felt to be in skeletal and cardiac muscle metabolism. Many of the symptoms of carnitine deficiency are due to depletion of carnitine stores in both cardiac and skeletal muscle, and improved energy and cardiac function have been reported following carnitine supplementation [26]. Ideally, carnitine deficiency should be diagnosed by a muscle biopsy, but it is possible to measure carnitine levels in the blood. In this context, both free and acyl carnitine can be measured, and carnitine deficiency is often reported to be present when the acyl carnitine (AC) to free carnitine (FC) ratio is greater than 0.4.

A role for carnitine has also been found in stabilising the red cell membrane. Thus, it is important for red cell survival, and the life-span of the red cell population may be reduced in carnitine-deficient states. Therefore, although carnitine is not directly implicated in erythropoiesis, it seems to have a role in maintaining the natural life-span of the red cell population.

In recent years, there has been some interest in the role of carnitine in patients receiving epoetin therapy. Kooistra et al [27] showed that the response to epoetin correlated with blood carnitine levels, with carnitine-deficient patients requiring the highest doses of epoetin. This led to the hypothesis that giving supplementary carnitine might augment the response to epoetin, and this has been the subject of several studies. The most widely quoted of these is the one by Labonia [28], in this study, patients received either L-carnitine or placebo for a period of 6 months. No change in epoetin dose requirements was seen in the placebo group, but the patients given L-carnitine had a 38% reduction in epoetin dose compared to baseline ( $p < 0.02$ ) (Fig. 4).

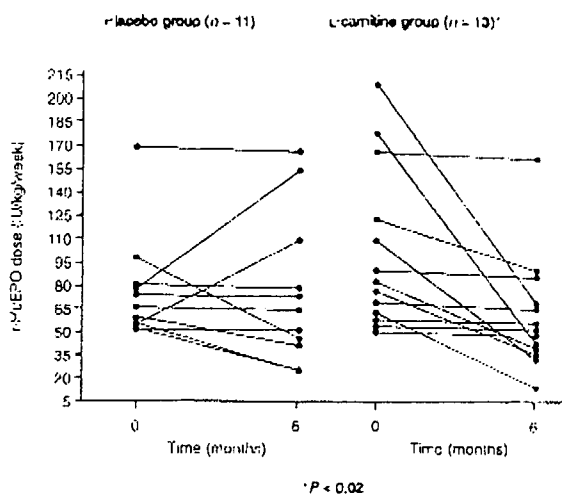


Fig. 4. Effect of 6 months of treatment with L-carnitine or placebo on r-HuEPO dose requirements [28].

In this study, there was no detectable change in red cell osmotic fragility or endogenous epoetin secretion. A study by Matsumura et al [29], however, confirmed a correlation between epoetin dose and free carnitine levels, in addition to showing increased red cell osmotic fragility in patients with a low L-carnitine level. Administration of L-carnitine has also been found to reduce erythrocyte membrane fragility in dialysed patients [30]. As with vitamin D supplementation, further controlled studies of carnitine supplementation are required before the exact role of this treatment strategy can be elucidated.

### Androgens

It has been recognised for several decades that androgens promote erythropoiesis, and this was put to therapeutic use in the 1970 before epoetin therapy was available. Dialysis patients often showed an improvement in their anaemia with androgen supplementation, although the treatment tended to be effective in mild cases only. There are two suggested mechanisms for this effect: (1) androgens can

enhance endogenous erythropoietin production; and (2) androgens may increase the sensitivity of erythroid progenitor cells to erythropoietin [31].

With the advent of epoetin therapy in the late 1980, several workers investigated whether androgens could potentiate the effect of epoetin in dialysis patients [31,32]. One of the earlier studies involved treating 15 adult male haemodialysis patients with epoetin 2000 units thrice weekly, with or without the addition of 100mg nandrolone decanoate intramuscularly each week [31]. After 12 weeks of therapy, the haematocrit had increased slightly in the group receiving epoetin alone (25.3% to 27.4%), but there was a much more marked response in the group receiving combination therapy (24.4% to 32.9%;  $p < 0.001$  vs. epoetin alone).

In a longer-term study, Gaughan et al [32] treated 11 male and 8 female patients on haemodialysis.

One group received epoetin alone (1500 units thrice weekly for 6 months), and the other group received the same dose of epoetin along with nandrolone decanoate 100mg intramuscularly each week. Both groups showed significant increases in mean haematocrit levels compared with baseline, but there was a much greater increase in the androgen-treated group compared with the group receiving epoetin alone (8.2% vs. 3.5%;  $p=0.012$ ). Not all studies, however, have shown a positive effect of androgen supplementation. In a controlled study by Bems et al [33], no difference in the response to intravenous epoetin (120 U/kg/week) was seen with the addition of intramuscular nandrolone decanoate 2mg/kg/week over a 16-week period.

There are two concerns about using androgen adjuvant therapy. The first is the high incidence of side-effects, including virilisation, hirsutism, voice changes, acne, cholestasis, and hepatic damage. There is also a concern that androgens may increase the risk of prostatic carcinoma, and for this reason some authors have recommended that the use of androgens be confined to men aged over 50 years. There has, however, been much interest in the potential role of androgens in augmenting the response to epoetin in countries with limited financial resources. Cost-benefit studies have not been performed, but it is possible that the combination of low-dose epoetin and androgen therapy may be cheaper than using epoetin alone.

### Other cytokines / growth factors

Although erythropoietin is the major regulator of red cell production, a number of other cytokines and growth factors are known to be involved in this process. Some of these act at an early stage of red cell differentiation, such as stem cell factor and interleukin-3, and a role for other factors such as interleukin-10 and insulin-like growth factor-1 has also been identified. Insulin-like growth factor-1 has been known to stimulate erythropoiesis since 1982 [34]. Erythroid progenitor cells possess IGF-1 receptors, and it is via this

mechanism that growth hormone can exert its effect on erythropoiesis.

Brox et al [35] have studied the use of IGF- I as an adjunct to epoetin in 5/6 nephrectomised mice.

The animals were given sub-therapeutic doses of epoetin, IGF- I, or the combination of the two.

Neither epoetin or IGF-I on its own caused any significant change in haemoglobin, but the combination resulted in correction of anaemia in the majority of mice treated. Indeed, the response to combination therapy was similar to that seen with the maximal dose of epoetin in a dose-finding study [35]. These results suggest that the combination of epoetin and IGF- I could be beneficial in renal patients, but no human studies are as yet available.

Similarly, interleukin-3 is known to potentiate erythropoiesis, and indeed a deficiency of this cytokine has been suggested as a cause of epoetin resistance [36]. Interleukin-3 acts by increasing the number of colonies derived from BFU-E which results in an expansion of the erythroid progenitor cell pool [37]. In vitro studies in patients with renal anaemia receiving epoetin therapy showed enhanced growth of BFU-E when IL-3 was added to the culture medium [38]. An in vivo study has also shown potentiation of IL-3 on erythropoiesis [39]. In this latter study, rabbits were rendered uraemic and anaemic by 5/6 nephrectomy; one group was then treated with epoetin alone while the other group received epoetin plus interleukin-3. The latter group showed a greater increase in haemoglobin concentration over the next 2-3 weeks [39].

## Conclusions

Thus, it is clearly possible to potentiate the response to epoetin by co-administering other agents.

In some instances, this response is seen when there is a deficiency of a certain substance. In other cases, administration of an adjuvant such as IV iron, vitamin D, L-carnitine, or androgens can enhance the response to epoetin when given as a surfeit. The role of the various adjuvants described in this paper is summarised in table 3 in relation to both deficiency and replete states. With most of these agents, with perhaps the exception of intravenous iron, further research is required to determine the exact role they may play in clinical practice. As long as the cost of epoetin therapy remains fairly high, the challenge will continue as to the best way of optimising its effect, and we can look forward to new developments in this expanding area of research.

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