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Experience with the Use of an Iron Polymaltose (Dextrin) Complex Given by Single Total Dose Infusion to Stable Chronic Haemodialysis Patients

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Key Words

Intravenous iron · Total dose infusion · Haemodialysis · Iron polymaltose · Iron dextrin

Abstract

Background: Many studies of anaemia in patients on chronic haemodialysis have noted a high prevalence of iron deficiency despite oral iron supplementation. Our study examined the effect of intravenous iron given as bolus replacement. As the majority of these patients were not receiving concurrent recombinant human erythropoietin (rhEPO) it allowed an analysis of the safety and efficacy of intravenous iron as a single agent. ***Methods:*** All patients with a haemoglobin level of less than 10 g/dl and considered iron deficient by the finding of a percentage transferrin saturation of less than 20% were given intravenous iron in the form of iron polymaltose (dextrin) by total dose infusion (TDI). The dose was calculated from tables supplied by the manufacturers. Patients with serum ferritin levels in excess of 225 ng/ml were excluded. ***Results:*** In our unit, 62 out of 80 (77%) patients were considered iron deficient and received IV iron. Ten (10%) were considered to be in iron balance and 8 (10%) had biochemistry suggesting iron overload. None of the patients receiving iron experienced any adverse reactions. At three months a rise in haemoglobin level of at least 1 g/dl was noted in 53% of patients. The response was less in the remainder, but only 2 showed no response. ***Conclusions:*** Low levels of iron deficiency are often unrecognized in chronic haemodialysis patients on conventional therapy including oral iron supplementation. In such patients, the use of total dose infusion of iron polymaltose (dextrin) is a safe and effective method of raising haemoglobin levels. Substantial improvements may be achieved without the concurrent use of rhEPO.

Introduction

Anaemia is almost always present in patients with severe chronic renal failure [1]. Its assessment and management becomes more complex once chronic haemodialysis (HD) is initiated. Factors such as inadequate dialysis, defective utilization of iron sequestered in body iron stores, poor absorption of dietary iron, gastrointestinal

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blood and dialysis-related blood loss [2, 3], aluminum toxicity [4], bone marrow fibrosis, vitamin and iron deficiency have been implicated.

With inadequate dialysis, anaemia requiring repeated blood transfusions may develop and in the past has resulted in iron overload in up to 25% of cases [1]. With modern dialysis and adequate attention to all reversible causes of anaemia, patients on chronic HD should have haemoglobin levels of at least 8 g/dl and with the additional use of recombinant erythropoietin (rhEPO), normal haemoglobin levels may be obtained [5]. With intensive rhEPO therapy, insufficient iron both in the form of inadequate stores or 'functional iron deficiency' may become the major limiting factor in achieving optimal haemoglobin levels [6]. With functional iron deficiency biologic availability of iron is reduced despite the presence of adequate storage iron. It may be demonstrated clinically by a response to IV iron in some patients with ferritin levels as high as 1,000 ng/ml [5, 6].

In our unit the use of rhEPO is severely limited because of financial restrictions. We were therefore able to examine the response to and safety of total dose iron infusion of an iron dextrin preparation given to a group of iron deficient patients not receiving concurrent rhEPO.

Patients and Methods

Iron deficiency was defined by transferrin (Tf) saturation levels of less than 20%, in the presence of a serum ferritin level of less than 225 ng/ml. The following were routinely measured: serum iron (SI), total iron binding capacity (TIBC), mean cell volume (MCV), mean cell haemoglobin (MCH), plasma albumin, calcium, inorganic phosphate, alkaline phosphatase and, if hyperparathyroidism was suspected, serum parathyroid (PTH) levels. As a measure of dialysis efficacy, a urea reduction ratio (URR) was done and expressed as a percentage. All blood samples were taken immediately before dialysis.

Patients

Of 80 patients, 62 (77%) were defined as being 'iron deficient' with the remainder having either normal or elevated iron levels. The 62 iron deficient patients were given intravenous iron by TDI and included in the study on efficacy and safety. During the study, 26 patients were excluded from the efficacy analysis for the following reasons: patients receiving renal transplants (4); blood transfusions given during follow-up (6); medical dialysis problems (4); rhEPO commenced as part of another study (6); death (1); incomplete data (2) and iron not given according to the protocol (3). None of the patients entered into the safety analysis were excluded.

The response to iron was studied in 36 patients including two patients who received rhEPO at a constant dose for the duration of the study, called the study group (SG). Patients who experienced a rise in haemoglobin, by the end of the study period, in excess of 1 g/dl were designated as the responder group (RG) and the remainder as the non-responder group (NRG). The SG consisted of 12 males and 24 females with a mean age of 40 years (range 20–61 years), mean duration on dialysis before the study was 27 months (range 1–127 months), mean number of units of blood given before the study was 6 (range 0–43 units), mean urea reduction ratio for the group was 67% (range 48–84%), mean serum albumin was 41 g/l (range 32–48 g/l), mean serum alkaline phosphatase 126 u/l (range 37–993 u/l) (normal range 30–115 u/l).

On completion of each dialysis session, patients routinely received vitamin C, folic acid, vitamin B complex, vitamin B12 and 200 mg of iron as oral ferrous sulphate. Calcium carbonate was the preferred phosphate binder except where elevated calcium levels necessitated the use of aluminum hydroxide (17 patients). Twenty two patients were taking 1-alpha hydroxy vitamin D_3 to elevate serum calcium and suppress parathyroid hormone secretion. Nine patients had previously undergone parathyroidectomies for tertiary hyperparathyroidism. Fifteen patients had radiologic evidence of renal osteodystrophy. PTH levels ranged from 5 to 1,000 pg/ml, mean 400 pg/ml (normal range 12–72 pg/ml).

Laboratory Methods

SI was determined by an automated system (BM/Hitachi System 704). TIBC was done by saturating transferrin binding sites with iron added to plasma. Excess unbound iron is then removed and plasma iron is measured by the assay for SI as described above. Serum ferritin was assayed using an immunoturbidometire method in an automated system (Tina-quant®, Boehringer Mannheim). All tests were done at the start of the study and thereafter on a monthly basis. Urea Reduction Ratios (URR) were done three-monthly, using the formula:

$$URR = {}^{Pre\text{-}Post}/_{Pre} \times 100\%$$

(where Pre = urea level at commencement of dialysis and Post = urea level 10 min after completion of dialysis).

Treatment Regimen

Patients were treated with an iron polymaltose (dextrin) preparation (Ferrimed®, Vifor International Inc., Switzerland). The dose required was calculated according to body mass and haemoglobin concentration using a table supplied by the manufacturer and was given as a total dose infusion (TDI). The dosage required ranged from 18 to 64 ml (900–3,200 mg of iron) and was diluted in 500 ml of normal saline and infused over a 4-hour period during a dialysis session.

Clinical Monitoring for Adverse Reactions

Blood pressure and pulse were measured hourly during the 4-hour dialysis period and temperature at commencement and at the end of the 4-hour infusion. Patients were told to report any symptoms that developed during or after the infusion period or between dialysis sessions.

Statistics

Data are reported as mean ± SD, graphs are mean ± 1 SE. Hypotheses about differences between means were analyzed using a paired t test (significance: $p < 0.05$).

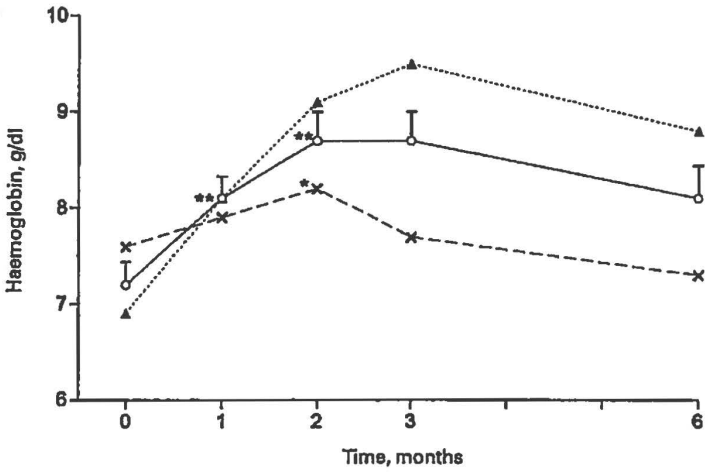

Fig. 1. Response in haemoglobin after total dose infusion (means ± SE). ○ = Whole study group (SG), n = 36; ▲ = response group (RG), n = 19; × = non-response group (NRG), n = 17. * $p < 0.05$ baseline versus month after infusion; ** $p < 0.001$ baseline versus month after infusion.

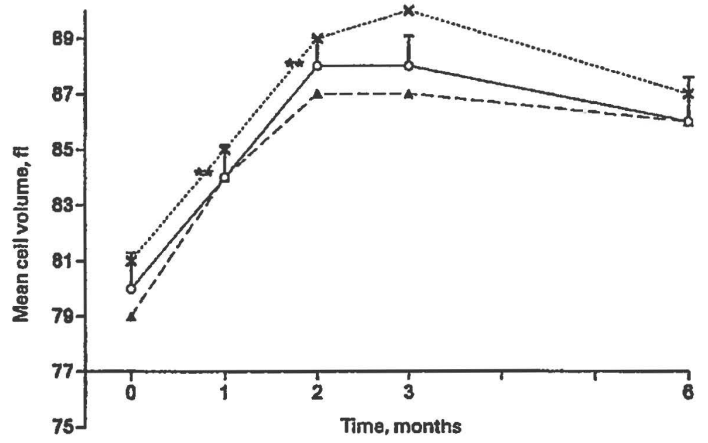

Fig. 2. Response in mean cell volume (MCV) after total dose infusion (means ± SE). ○ = Whole study group (SG), n = 36; ▲ = response group (RG), n = 19; × = non-response group (NRG), n = 17. * $p < 0.05$ baseline versus month after infusion; ** $p < 0.001$ baseline versus month after infusion.

Results

The Effect of Iron Infusion on Haemoglobin Concentration

Three months after the total dose infusion in the SG, n = 36, 19 patients (53%) had experienced a rise in haemoglobin of at least 1 g/dl and were defined as the RG. The remaining 17 (47%) formed the NRG (fig. 1).

Only two patients of the entire study group failed to show at least some rise in haemoglobin, one remained unchanged and the other had a drop in haemoglobin of 1 g/dl. Twelve patients attained haemoglobin levels of greater than 10 g/dl.

The Effect of Iron Infusion on Mean Cell Volumes, Mean Cell Haemoglobin, Transferrin Saturation and Serum Ferritin (fig. 2–5)

Rises in MCV ranged from a minimum of 4 fl (included are some patients with starting MCV of as high as 92 fl) to a maximum rise of 16 fl. Changes in MCH were

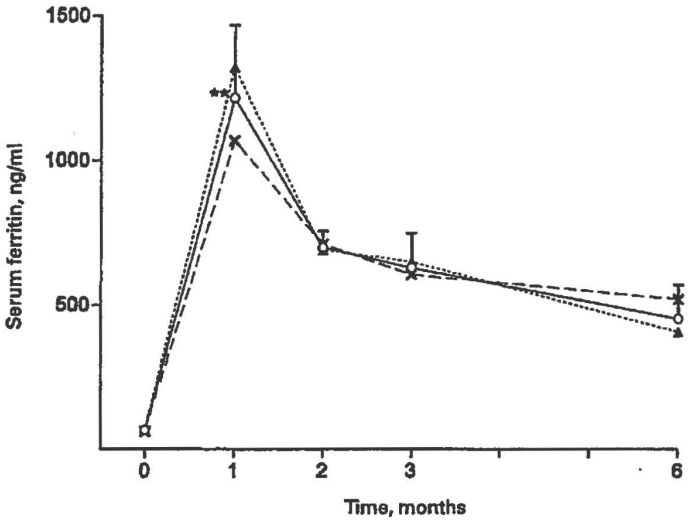

Fig. 3. Response in mean cell haemoglobin (MCH) after total dose infusion (means ± 1 SE). ○ = Whole study group (SG), n = 36; ▲ = response group (RG), n = 19; × = non-response group (NRG), n = 17. * $p < 0.05$ baseline versus month after infusion; ** $p < 0.001$ baseline versus month after infusion.

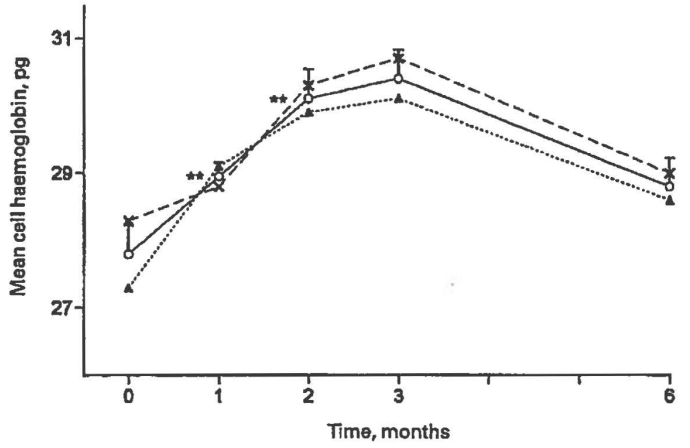

Fig. 4. Response in transferrin saturation after total dose infusion (means ± 1 SE). ○ = Whole study group (SG), n = 36; ▲ = response group (RG), n = 19; × = non-response group (NRG), n = 17. * $p < 0.05$ baseline versus month after infusion; ** $p < 0.001$ baseline versus month after infusion.

similar to those seen with the MCV. By 6 months Tf saturation had dropped to below 20% in 13 patients and ferritin to below 225 ng/ml in 15.

In order to determine if factors were present which might affect the magnitude of the response, RG was further subdivided into RG_1 (12 patients), a group with a haemoglobin rise of at least 2 g/dl and group RG_2 (7 patients) with a haemoglobin rise of at least 3 g/dl (table 1). Besides the rise in haemoglobin, other differences were small and confined to a slightly higher starting haemoglobin and MCV in the NRG. Indices of iron balance were similar. A comparison of baseline parameters was also made (table 2). By comparison to the NRG, the RG had fewer units of transfused blood (3.1 vs. 8.6), had higher serum albumin levels (42.5 vs. 39.7 g/l) and slightly less efficient dialysis as reflected by a lower URR.

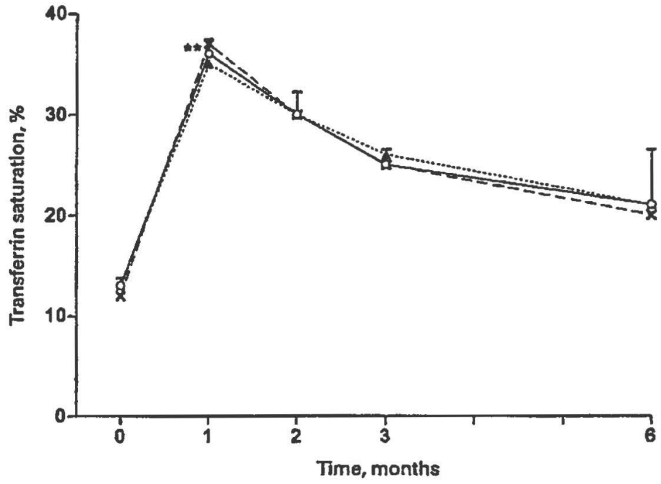

Fig. 5. Response in serum ferritin after total dose infusion (means ± 1 SE). ○ = Whole study group (SG), n = 36; ▲ = response group (RG), n = 19; × = non-response group (NRG), n = 17. * $p < 0.05$ baseline versus month after infusion; ** $p < 0.001$ baseline versus month after infusion.

Table 1. Response to intravenous iron

	RG n = 19	RG_1 n = 121	RG_2 n = 7	NRG n = 17	TG n = 55
Haemoglobin (Bl)	6.9 (1.3)	6.4 (1.2)	6.2 (1.2)	7.7 (1.5)	6.9 (1.3)
Month 1	8.2 (1.0)	8.0 (1.1)	8.4 (1.1)	7.9 (1.7)	8.1 (1.3)
Month 2	9.1 (1.5)	9.0 (1.8)	9.6 (2.2)	8.2 (2.0)	8.9 (1.8)
Month 3	9.5 (1.5)	9.6 (1.8)	10 (2.1)	7.7 (1.6)	9.0 (1.7)
Month 6	8.8 (1.5)	9.0 (1.7)	8.9 (2.0)	7.3 (1.9)	8.4 (1.7)
MCV (Bl)	79 (9.5)	77 (10)	76 (13)	81 (6.8)	78.8 (9.2)
Month 1	84 (6.9)	83 (6.5)	82 (7.9)	85 (6.3)	83.8 (6.8)
Month 2	87 (7.2)	86 (7.0)	86 (9.1)	89 (4.9)	87.3 (6.7)
Month 3	87 (7.4)	86 (6.8)	85 (8.3)	90 (5.9)	87.5 (6.9)
Month 6	86 (10.2)	84 (9.8)	84 (11.7)	87 (4.0)	85.6 (8.4)
MCH (Bl)	27.3 (2.7)	26.9 (2.3)	27.0 (1.2)	28.3 (2.5)	27.5 (2.4)
Month 1	29.1 (2.3)	26.0 (2.2)	29.2 (1.4)	28.8 (2.2)	29.0 (2.1)
Month 2	29.9 (2.8)	29.1 (2.5)	29.3 (1.9)	30.3 (2.5)	29.8 (2.5)
Month 3	30.1 (2.6)	29.9 (2.2)	29.7 (2.3)	30.7 (2.5)	30.2 (2.4)
Month 6	28.6 (2.3)	29.4 (2.0)	30.0 (1.1)	29.0 (2.8)	29.1 (2.2)
Transferrin sat (Bl)	12.2 (4.4)	12 (4.3)	11 (4.1)	13 (5.4)	12.3 (4.6)
Month 1	37.4 (21.4)	37 (22.7)	31 (12.8)	35 (19)	35.8 (19.8)
Month 2	30.5 (15.8)	34 (17.5)	31 (4.2)	30 (9.5)	31.2 (12.7)
Month 3	24.7 (7.6)	25 (6.3)	24 (4.1)	26 (10)	25.1 (7.6)
Month 6	20.3 (8.7)	19 (8.9)	20 (10.7)	21 (7.4)	20.2 (8.6)
Serum ferritin (Bl)	63 (60)	74 (69)	71 (73)	72 (52)	69 (61)
Month 1	1,069 (481)	1,099 (534)	750 (429)	1,320 (1,581)	1,113 (826)
Month 2	712 (477)	838 (518)	713 (404)	690 (452)	733 (469)
Month 3	606 (451)	688 (527)	927 (647)	651 (641)	679 (551)
Month 6	521 (664)	819 (1,013)	250 (332)	408 (342)	517 (598)

RG = Responding group; RG_1 = mean haemoglobin response of >2 g/dl; RG_2 = mean haemoglobin response of >3 g/dl; NRG = mean haemoglobin rise of <1 g/dl; TG = total group; Bl = baseline. Data are mean (SD).

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