ERYTHROPOIETIN IN THE TREATMENT OF ANAEMIA OF CHRONIC RENAL FAILURE

(Received 21 May, 1993)

İ.Ç. Özener, M.D.* / R.A. Lawrence, M.D.****
Ö. Ersöz, M.D. *** / E. Akoğlu, M.D.***

* *Professor, Department of Internal Medicine, Faculty of Medicine, Marmara University, İstanbul, Türkiye.*
** *Assistant Professor, Department of Internal Medicine, Faculty of Medicine, Marmara University, Istanbul, Türkiye.*
*** *Specialist, Department of Internal Medicine, Faculty of Medicine, Marmara University, Istanbul, Türkiye*
**** *Research Assistant, Department of Internal Medicine, Faculty of Medicine, Marmara University, Istanbul, Türkiye.*

SUMMARY

Human recombinant erythropoietin was administered subcutaneously to 26 chronic haemodialysis patients over a six month period, and the effect of erythropoiesis investigated. Initial therapy was 4000 units twice weekly with therapy titrated to individual response after 1 month. Mean EPO dosage was 150 ± 51 u/kg/week at the start of the study and 112 ± 50 u/kg/week at 6 months. The mean haemoglobin level rose from 6.7 ± 1.7 gr/dl at the start of treatment to 9.1 ± 1.9 gr/dl at 3 months ($p<0.01$) and 9.6 ± 1.9 gr/dl at 6 months. Simultaneously the mean haematocrit rose from 21 ± 4.8 to 28.3 ± 6.2 at 3 months ($p<0.01$) and 29.3 ± 4.6 at 6 months. Platelet count and white cell count were unaffected by therapy. Treatment failure occurred in 5 patients and seizures were seen in 4 patients. EPO therapy was not associated with increase in blood pressure.

Key Words : Anaemia, erythropoietin, chronic renal failure, haemodialysis

INTRODUCTION

Anaemia is one of the most common findings in patients with chronic renal insufficiency. As the creatine clearance decreases haemoglobin levels also drop until in end stage disease seriously incapacitating anaemia may occur (1). Many of the problems of chronic renal failure patients receiving dialysis therapy are consequences of anaemia and even when adequate dialysis is given to the patient anaemia persists and significantly reduces the patients quality of life (2).

The most important cause of anaemia in the haemodialysis population is reduced production of erythropoietin by the patient's native kidneys. Other causes include decreased red cell survival secondary to haemolysis, iron and water soluble vitamin deficiencies, supression of haemopoiesis secondary to aluminium toxicity, secondary hyperparathroidism and various uraemic inhibitors, and loss of blood occurring during dialysis or associated with over zealous blood sampling (3-5).

In the past blood transfusions and androgenic steroids have been used with only limited response in this group of patients (4,5). Recently human recombinant erythropoietin (rHuEPO) has been used with great success in the treatment of anaemia of chronic renal failure.

This study was designed to examine the efficacy and safety of rHuEPO therapy in a population of patients undergoing regular haemodialysis treatment at Marmara University Hospital Haemodialysis Unit.

MATERIALS AND METHODS

The study population consisted of 26 patients (13 males and 13 females) undergoing chronic haemodialysis at our unit and with a serum haemoglobin concentration of less than 9 gr/dl. Patients ranged from 19 to 74 years of age with a mean age of 44 ± 16 years.

The primary causes of renal failure in this group of patients were chronic glomerulonephritis (10 patients), chronic pyelonephritis (8 patients), hypertensive nephrosclerosis (3 patients), diabetic nephropathy (2 patients), polycystic kidney disease (2 patients), and post partum nephropathy (1 patient). One patient with chronic pyelonephritis, reflux, and recurrent urinary tract infection had undergone bilateral nephrectomy. Twenty patients had previously received transfusions of between one and ten units of blood. Patients had been receiving 4 hours haemodialysis 2 or 3 times weekly for between 6 months and 5 years. One patient had a history of epilepsy. Patients with anaemia unrelated to haemodialysis (eg. gastrointestinal bleeding) were excluded from the study.

All patients enrolled onto the study were administered regular vitamin B complex and iron supplementation. Patients with high serum inorganic phospate levels were treated with Aluminium hydroxide 3 x I gr.

Prior to commencement of EPO therapy all patients had blood sampled for estimation of serum haemoglobin, haematocrit, white blood cell count, platelet count, routine biochemical parameters

(including blood urea nitrogen, serum creatinine and electrolytes and liver enzymes), serum ferritin levels, and iron binding capacity. These parameters were measured at monthy intervals throughout the trial.

Blood pressures were recorded prior to each dialysis session with the patient rested for 10 minutes by a dialysis nurse using a mercury sphgynomanometer. All antihypertensive therapy was noted, together with any changes in therapy.

Patients received 4000 units rHuEPO twice weekly following haemodialysis via the subcutaneous route in the forearm. The therapeutic target was an increase in the haematocrit to a value of 30%. Following the first month of therapy EPO dosage for individual patients was titrated according to each individual's response to therapy.

Any medical problems, changes in blood pressure and haemodialysis or vascular access related problems occurring within the study period were noted.

Results were analysed using Student's paired and unpaired t tests.

RESULTS

The patient's mean serum haemoglobin concentration at the start of the trial was 6.7 ± 1.7 gr/dl rising to 9.1 ± 1.9 gr/dl at 3 months and 9.6 ± 1.9 gr/dl at 6 months. Levels at both 3 and 6 months were significantly raised over the pre-treatment level ($p<0.01$), but levels at 3 and 6 months were not statistically different from one another. Mean haematocrit values at 0, 3 and 6 months were 21 ± 4.8 %, 28.3 ± 6.2%, and 29.3 ± 4.6% respectively. The rise in haematocrit seen at 3 and 6 months was significantly raised over the baseline value ($p<0.01$), but again the values at 3 and 6 months were not significantly different from one another (Fig 1.)

The mean white cell counts at 0, 3 and 6 months were 6.4 ± 2.4 x 10^3 / mm^3, 5.9 ± 2 x 10^3 / mm^3, and 6.4 ± 3.3 x 10^3 / mm^3, respectively and did not vary significantly during the course of the trial.

Similarly thrombocyte counts did not vary significantly throughout the study period with 0, 3, and 6 months counts of 189 ± 64 x 10^3 / mm^3, 162 ± 63 x 10^3 / mm^3, and 178 ± 70 x 10^3 / mm^3 respectively.

Mean systolic and diastolic blood pressures remained unchanged by therapy.

No changes in mean blood urea nitrogen, serum creatinine, or electrolytes including calcium or inorganic phosphate were observed.

Although EPO dosage was deliberately reduced over the study period the mean EPO dosages did not differ statistically significantly, 0, 3 and 6 month mean

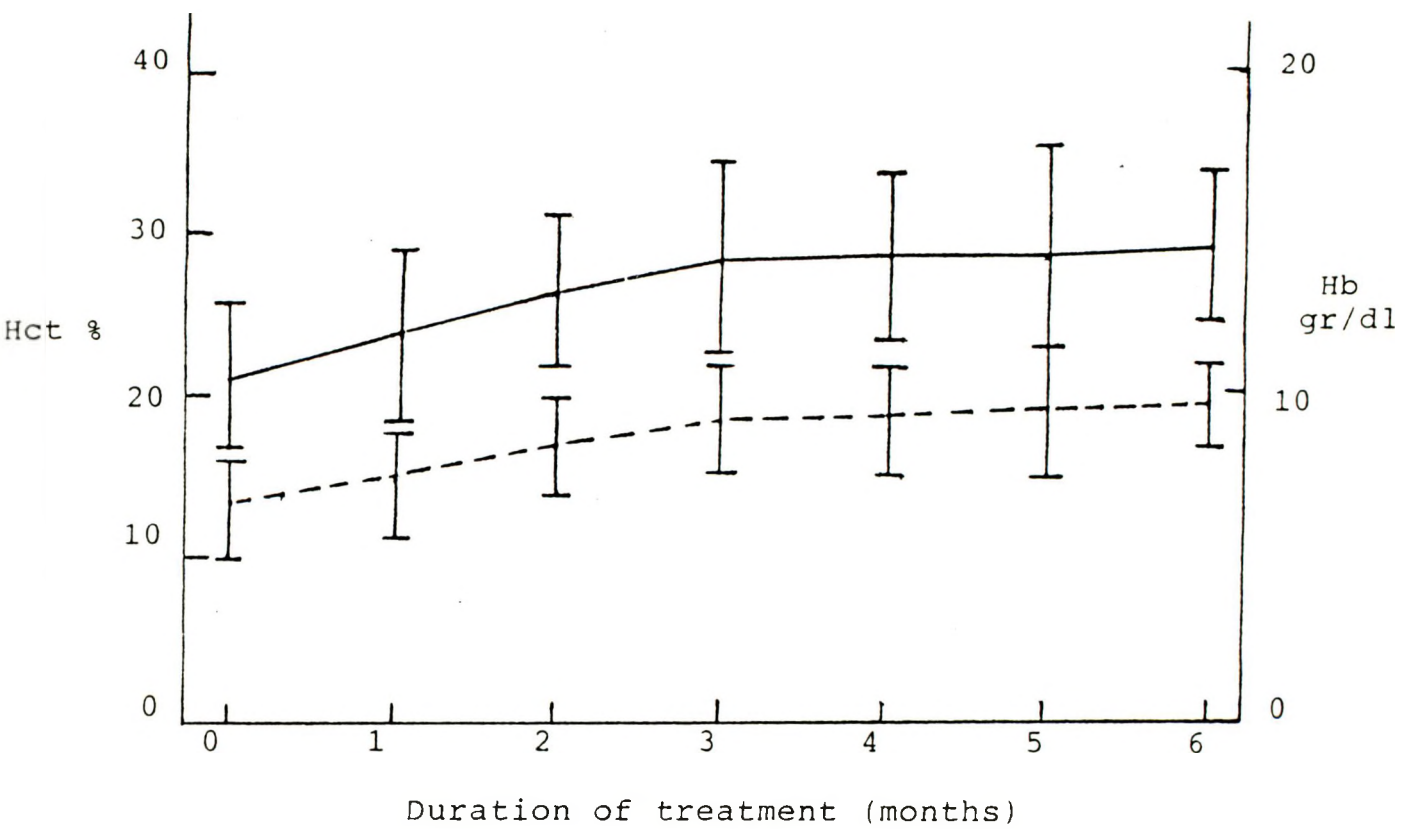

Fig 1. Haematocrit [———] and haemoglobin [– – –] concentrations (mean ± SEM) measured at monthly intervals during the study.

dosages being 130 ± 51 u/kg/week, 122 ± 56 u/kg/week and 112 ± 50 u/kg/week respectively. This failure to achieve significance relects the size of the study population.

The only serious side effect of therapy was fitting which was observed in four patients and controlled with diphenylhydantoin. Pain around the injection site at the time of administration was a common complaint.

Treatment failure was observed in 5 patients. In three patients it was total with no increase in haemoglobin concentration or haematocrit observed. In the other two patients' haemoglobin levels rose by 0.8 and I gr/dl.

All of the 21 patients treated succesfully with EPO reported improvement in appetite and effort capacity, and feelings of increased well being.

DISCUSSION

The ideal treatment of end stage failure and therefore the problems, including anaemia, which are associated with it, is renal transplantation. In a large group of patients transplantation is either not possible or unsuccessful and these patients may spend many years receiving haemodialysis therapy. The anaemia present in these patients is detrimental to the quality of their lives, and contributes significantly or is responsible for a number of their symptoms.

Human recombinant erythropoietin has been successfully used in the treatment of anaemia of renal failure (6-10). In this study, as in other studies, EPO administration resulted in a significant rise in mean patient haemoglobin levels (from 6.7 ± 1.7 gr/dl to 9.6 ± 1.9 gr/dl) and haematocrit (from 21 ± 4.8% to 29.3 ± 4.6%), the target haematocrit value of 30% being closely approached.

At the commencement of EPO therapy mean dosage was 130 ± 51 u/kg/week. After 3 months when the targeted rise in haematocrit had been almost reached the EPO dosage had been reduced slightly to a mean of 122 ± 56 u/kg/week. By 6 months the further slight rise in haemoglobin and haematocrit levels was paralleled by a further slight reduction in mean EPO dosage. It is recognised that by the 3rd month of therapy haemoglobin and haematocrit levels stabilise and may be maintained with lover doses of EPO. In a European multicentre trial reported by Sundal haemoglobin levels had stabilised by the 16th week of EPO therapy and could be maintained at a mean intravenous dose of 200u/kg/week (11).

In the first clinical trials using rHuEPO administration was via the intravenous route (7,8,12) but later it was recognised that subcutaneous administration lengthens the half life of the hormone permitting dose reduction without loss of efficacy. More recently therefore, the preferred method of administration has been via the subcutaneous route (13-18), and has been employed in the present study.

As reported above treatment failure was seen in five patients. In two patients later treated by subtotal parathyroidectomy, the cause was thought to be severe secondary hyperparathyroidism. Raised serum parathormone levels lead to bone marrow depression and fibrosis, and may cause non response to EPO (19,20). One patient was found to have a serum aluminium level of 12.8 umol/L. There are a number of reports that elevation of serum aluminium values above the normal range of 0-1 umol/L inhibit the effects of EPO (21-23) probably by interfering with utilisation of iron. One patient was suffering from hepatic cirrhosis secondary to Hepatitis B infection. Lack of response was probably related to the hypersplenism exhibited by this patient. The last patient who failed to repond to therapy was found to be iron deficient with a serum ferritin level of 28 ugr/dl, serum iron level of 22 ugr/dl, and an iron binding capacity of 200 ugr/dl. This patient was unable to tolerate either oral or parenteral iron and did not respond to EPO therapy because of her continuing iron deficiency.

Winearls et al, in their original paper reported no effect of rHuEPO on thrombocyte or leukocyte counts (7). It has been reported that erythropoietin therapy improves the haemostatic defect in uraemics but that this is not associated with increased platelet counts (24). Berridge et al have however described EPO induced increases in thrombocyte counts in rats (25). Our results support those of Winearls, no significant change in either thrombocyte or leucocyte counts occurring during the course of the study.

There are reports decribing rises in blood pressure with occasional episodes of hypertensive encephalopathy. Sundal et al and Casatis et al report the incidence of worsening of blood pressure to be 8% and 7% respectively (11,26). Abraham and Esbach have stressed the role of high dose intravenous therapy with a subsequently rapidly rising haematocrit as factors likely to cause rises in blood pressure (27,28). Winearls et al have reported a higher incidence of worsening of hypertension in patients where the haematocrit has risen above 30% during therapy (7). The absence of changes in blood pressure in this study can be explained in the light of the low dose therapy administered and the decision not to raise haematocrit values above 30%.

One of the most important side effects of EPO therapy is the occurrence of grand mal epilepsy which occurs in between 1 and 7% of patients. Epileptic fits are most frequently reported to occur in the first three months of therapy and are not related to rises in blood pressure. Brain tomography (BT) and electroencephalography (EEG) are normal in this group (19,29,30).

In our study four patients (11.5%) suffered generalised seizures, all occurring in the first three months of therapy. Only one of these patients had a previous history of epilepsy. None of these patients had worsening of their blood pressure of electrolyte disturbances during attacks. Both BT and EEG were normal in all patients.

Table I- Haematological parameters (mean ± SEM) measured at 0, 3 and 6 months.

	Hb (gr/dl)	Hct	Platelet count ($x10^3$ / mm^3)	White cell count ($x10^3$ / mm^3)
Baseline	6.7 ± 1.7	21 ± 4.8	189 ± 64	6.4 ± 2.4
3 months	9.1 ± 1.9 *	28.3 ± 6.2*	162 ± 63	5.9 ± 2
6 months	9.6 ± 1.9*	29.3 ± 4.6*	178 ± 70	6.4 ± 3.3

* $p<0.01$

Patients were treated with diphenylhydantoin 200 mg daily in two divided oral doses and EPO therapy continued with no recurrence of attacks.

The pathophysiological mechanism responsible for seizures remains unclear, although it is known that EPO does not cross the blood brain barrier and EEG changes do not occur. It has been hypothesised that rapid increases in blood viscosity and accompanying changes in blood pressure may lead to alterations in cerebral blood flow and fitting (6,11,19).

In conclusion treatment of chronic haemodialysis patients with rHuEPO is an effective means of treating their anaemia. In addition to removing the need for blood transfusions the patients quality of life is improved (2). Low dose subcutaneous therapy results in a low rate of complications such as hypertension. The most important side effect of therapy is convulsions but these can be effectively controlled with oral diphenylhydantoin therapy without the need to discontinue EPO therapy.

REFERENCES

1. *Fyhraqist F, Rosenlof K, Gronhagen R C, et al. Is renin substrate an erythropoietin precursor? Nature 1984; 308:649-652.*
2. *Wolcott W, March J T, Rue A, et al. Recombinant human erythropoietin may improve quality of life and cognitive function in chronic hemodialyis patients. Am J Kidney Dis 1989; 14: 478-485.*
3. *Beserab A. Recombinant human erythropoietin: Physiology, pathophysiology of anemia in renal failure and economic aspects relating to dosing. Am J Nephrol 1990; 10 (Suppl 2): 2-6.*
4. *Bia M J, Cooper K, Schnall S, et al. Aluminium induced anemia: Pathogenesis and treatment in patients on chronic hemodialysis. Kidney Int 1989; 36: 852-858.*
5. *Rose B D, Black R M. Manual of clinical problems in nephrology 2nd edition. Boston: Little Brown Co, 1988: 357-370.*
6. *Abraham P A. Practical approach to initiation of recombinant human erythropoietin therapy and prevention and management of adverse effects. Am J Nephrol 1990; 10 (Suppl 2): 7-14.*
7. *Winearls C G, Oliver D O, Pippard M J, Reid C, Downing M R, Cotes P M. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. Lancet 1986; ii: 1175-1178.*
8. *Winearls. C G. Treatment of anaemia in haemodialysis patients with recombinant erythropoietin. Nephron 1989; 51 (Suppl 1): 28-29.*
9. *Bommer J, Alexiou C, Muller-Bühl U, Eifert J, Ritz E. Recombinant human erythropoietin in haemodialysis patients. Nephrol Dial Transpl 1987;2: 238-242.*
10. *Zehnder C, Gluck Z, Descoedres C, Uehlinger DE, Blumberg A. Human recombinant erythropoietin in anaemia patients on maintenance hemodialysis. Secondary effects of the increase of hemoglobin. Nephrol Dial Transpl 1989; 3: 657-660.*
11. *Sundal E, Kaeser U. Correction of anaemia of chronic renal failure with recombinant human erythropoietin. Safety and efficacy of one year's treatment in a European multicentre study of 150 haemodialysis-dependant patients. Nephrol Dial Transpl 1989; 4; 979-987.*
12. *Winearls C G. Use of erythropoietin in patients with end-stage renal failure. Royal Soc Med 1988; 1: 2-6.*
13. *Spinowitz B. The practical aspects of therapy with rHuEPO. Am J Nephrol 1990; 10 (Suppl 2) : 24-28.*
14. *Mahon G F, Vargas R, Ryan M et al. Pharmacokinetics and effects of recombinant human erythropoietin after intravenous and subcutaneus injections in healthy volunteers. Blood 1990; 76: 1718-1722.*
15. *Stevens J M, Auer J, Strong C A, et al. Stepwise correction of anaemia by subcutaneus administraion of human recombinant erythropoietin in patients with chronic renal failure maintained by continuous ambulatory peritoneal dialysis. Nephrol Dial Transpl 1991; 6: 487 - 494.*
16. *Lui S G, Chung W W M, Leung C B, Chan K, Lea K N. Pharmacokinetics and pharmacodynamics of subcutaneous and intraperitoneal administration of recombinant human erythropoietin in patients on continuous ambulatory peritoneal dialysis. Clin Nephrol 1990; 33: 47-51.*
17. *Stevens J M, Strong C A, Oliver D O, Winearls D G, Cotes P M. Subcutaneus erythropoietin and peritoneal dialysis. Correspondence Lancet 1989; I: 1388 - 1389.*
18. *Aronoff G R, Duff D R, Sloan R S, et al. The treatment of anemia with low dose recombinant human erythropoietin. Am W Nephrol 1990; 10 (Suppl 2): 40-43.*
19. *Schaefer R M, Hörl W H- Massry S G. Treatment of renal anemia with recombinant human erythropoietin. Am J Nephrol 1989; 9: 353-362.*

20. Drueke T B. resistance to recombinant human erythropoietin in haaemodialysis patients. Am J Nephrol 1990; 10 (Suppl 2): 34-39.
21. Losekann A, Urena P, Khiraoui F et al. Aluminium intoxication in the rat induces partial resistance to the effect of recombinant human erythropoietin. Nephrol Dial Transpl 1990; 5: 258-263.
22. Yaqoob M, Ahmad R, Roberts N, Helliwell T. Low-dose desferrioxamin test for the diagnosis of aluminium-related bone disease in patients on regular haemodialysis. Nephrol Dial Transpl 1991; 6: 484-487.
23. Muirhead N, Hodsman A B, Hollomby DJ, Cordy P E. The role of aluminium and parathyroid hormone in erythropoietin resistance in haemodialysis patients. Nephrol Dial Transpl 1991; 6: 342-346.
24. Mola M, Mannucci PM, Vizzotto L, Casati S, Caataneo M, Ponticelli C. Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin in man. Lancet 1987; ii: 1227-1229.
25. Berridge M V, Fraser J K, Carter J M, Lin FK. Effects of recombinant human erythropoietin on megacaryocytes and on platelet production in the rat. Blood 1988; 72: 970-977.
26. Casati S, Passerini P, Campise M R et al. Benefits ad risks of protracted treatment with human recombinant erythropoietin in patients having haemodialysis. Br Med J 1987; 295: 1017-1020.
27. Paine C J, Hargrove M D, Eichner E R. Folic acid binding protein and folate blance in uraemia. Arch Int Med 1981 136; 757.
28. Esbach J W, Kelly M R, Haley N R, Abels R I, Adamson R W Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. N Eng J Med 1989; 321: 158-163.
29. Edmunds M E, Walls J, Tucker B, et al. Seizures in haemodialysis patients treated with recombinant human erythropoietin. Nephrol Dial Transpl 1989; 4: 1065-1069.