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Human recombinant erythropoietin: Is it the missing ingredient in the full rehabilitation of dialysis patients?

A. P. Lundin
Health Science Center. Brooklyn. New York (USA).

In my personal experience with hemodialysis I would rank the following:

1. Arterio-venous fistula.
2. Recombinant erythropoietin.
3. Hollow fiber dialysis.
4. Synthetic 1,25 $(OH)_2D_3$.
5. Aluminum removal with Desferal^R.

Reliable access to the blood, highly efficient hemodialysis, and ability to modify renal osteodystrophy have all contributed to the long survival and considerable rehabilitation of many dialysis patients even as their anemia persisted. Will the use of recombinant human erythropoietin (r-HuEPO) with normalization of RBC mass and hematocrit (Hct) restore normal quality of life to the dialysis patient? Close, but not quite.

The dialysis patient will always be limited by the inherent restrictions of the treatment and by the fact that the internal body milieu can never be restored to normal except by 24 hour a day kidney function as provided by a kidney transplant. While both synthetic erythropoietin and active vitamin D have permitted exogenous replacement of several vital kidney functions and many patients have adapted remarkably well to the restrictions of dialytic therapy, the persistence of uremic toxins will always be a limiting factor.

Retained toxins contribute in a number of ways to the uremic syndrome as evidenced by at least partial reversal of these roles following institution of dialysis. Carbohydrate intolerance, platelet dysfunction, GI symptoms, and pericarditis, to name a few, are likely due to retained toxic metabolites. Highly efficient hemodialysis marked by a KT/V of ≥ 1.2 or a pre to post dialysis BUN reduction of ≥ 60 % will minimize the most obvious symptomatic effects of the uremic toxins. Some improvement of anemia, exercise capacity and overall sense of well-being will also be noted with efficient dialysis but they are not brought up to normal levels. Restoration of normal Hct levels with r-HuEPO, however, even without a further reduction of uremic toxins, has caused a dramatic improvement in exercise capacity, cardiac function, and quality of life for dialysis patients.

A number of studies have shown an increase in exercise capacity and improvement of cardiac function in hemodialysis patients following treatment with r-HuEPO [1-2]. We measured the VO_{2peak} of 10 patients before and after treatment with r-HuEPO. Over 91 days of treatment their hemoglobin levels increased from 7.1 gm/dl to 9.8 gm/dl with a corresponding rise in VO_{2peak} from 15.1 ± 5.3 ml O_2/kg/min to 22.7 ± 4.6 ml O_2/kg/min ($p < .05$) [3]. Even though our patients advanced from a below normal range to a low normal range for exercise tolerance they still continued to exhibit leg fatigue as a limiting factor for exercise. This causes us to suspect that a r-HuEPO induced rise in Hct cannot overcome the effects uremic toxins as a source of leg fatigue. We feel that dialysis patients, because of premature leg fatigue, do not reach a VO_{2max} but only a VO_{2peak} [4]. Therefore patients on dialysis even if treated by r-HuEPO will continue to have an impaired exercise capacity, normalized only by 24 hour per day full kidney function.

Several other impressive benefits of r-HuEPO are realized when patients are questioned about other conditions of their lives (Table 1) [5]. Many dialysis patients complain that daily activities are often tiring requiring extra effort with fitful night sleep and daytime napping. Sexual function and appetite are often described as poor. Improvement is found in all of these areas with a rise in Hct. Perhaps improvement is due to greater energy levels with more activity during the day. However, almost half or more of patients also described improvements in hair thickness, fingernail growth, and taste for food, and cold tolerance (often noticed when feeling too hot indoors due to the extra

Correspondencia: A. Peter Lundin, MD.
Associate Professor of Medicine.
Suny, Health Science Center at Brooklyn.
450 Clarkson Ave.
Box 52.
Brooklyn, New York 11203.

Table I. Subjective benefits of r-HuEPO in hemodialysis patients

	No. of patients (%)			
	Before EPO		After EPO	
Daily activities	Tiring	32 (71.1)	Better	37 (82.2)
Sleep habits	Poor, fair	42 (93.3)	Good	38 (84.4)
Day napping	Frequent	26 (57.7)	Rare	33 (73.4)
Sexual function	Poor	39 (86.7)	Good	25 (55.6)
	Average	6 (13.3)	Very good	8 (17.8)
Appetite	Poor	28 (62.2)	Good	41 (91.1)
Cold tolerance			Improved	39 (86.7)
Hair thickness			Improved	20 (44.4)
Fingernail growth			Improved	21 (46.7)
Taste for food			Improved	39 (86.7)
Skin color			Improved	41 (91.1)

clothing they formerly needed): additional effects of an increase in the oxygen carrying capacity of the blood. Lastly patients were pleased with the loss of skin pallor and the improvement of color. Objective improvements in cognitive function have been noted with r-HuEPO treatment[6]. Corresponding to patient claims of improvement in sexual function with r-HuEPO have been reductions in prolactin levels elevations of which have been thought to contribute to sexual dysfunction in chronic renal failure[7]. The impressive resolution of uremic symptoms seen with r-HuEPO might cause on to suspect that much of the uremic syndrome is due to anemia.

In the current state of r-HuEPO euphoria, however, one should not overlook the fact that uremic toxins persist and that the use of r-HuEPO is not without potential risks. Symptomatic improvement with a rising Hct might only mask symptoms which would indicate that subadequate dialysis is being prescribed. Moreover, a higher Hct could contribute to reduced dialysis efficiency. Dialyzable uremic toxins are removed directly only from plasma water which is proportionally reduced as Hct is raised. Preliminary studies indicate that dialysis efficiency is reduced with higher Hcts[8]; moreover, a marginally adequate dialysis might become subadequate with only a small reduction in efficiency. Any shortening in dialysis time with higher Hcts will require substantial increases in dialyzer efficiency to prevent inadquate dialysis. With dialyzer reuse the increased viscosity of blood at a higher Hct, passing through fibers clogged with protein, could result in the decreased clearance of small and middle molecules during dialysis. These possibilities need to be carefully monitored.

As appetite improves it can be expected that patients will become less cognizant of dietary restrictions and eat more. This has been noted with a rise of predialysis serum BUN, potassium (K^+) and phosphate (P) levels[9]. Awareness of this problem should lead to early dietary counselling. Better would be to increase dialysis efficiency and lower the K^+ concentration of the bath, reducing only excessive protein, K^+ and P ingestion. Improved patient nutrition would be another beneficial outcome of r-HuEPO.

Rapid increases in Hct due to overtreatment with r-HuEPO have led to hypertension[10]. Cautious elevation of the Hct should be the order of the day. In the absence of active blood loss, hemolysis, or marrow

Table II. Treatment of hemodialysis patients with r-HuEPO

1. Make sure:
   a) There is no active bleeding or hemolysis.
   b) Iron stores are adequate.
   c) There are no other treatable causes of anemia.
2. Start with dose of 2000 to 4000 units IV or SC.
3. Check reticulocyte count:
   a) If brisk (3-6 %), maintain dose to desired Hct.
   b) If low (< 2 %), increase dose by 1000 units.
   c) If high (> 8 %) and Hct is rising rapidly, reduce dose.
4. When desire Hct level is nearly reached:
   a) Reduce EPO dose by 500-1000 units.
   b) When Hct falls, increase dose by smaller increments.

Table III. Use of reticulocyte count

Reticulocytosis		No reticulocytosis
Rise in Hct	Stable Hct	
Normal	1. Blood loss	1. Fe deficiency
	2. Hemolysis	2. Al^{+++} intoxication
		3. Osteitis fibrosa
		4. Myelodysplasia
		5. Chronic inflammation
		6. Sideroblastic anemia

suppression it should be fairly simple to interdict the need for RBC transfusions. Patients needing a higher Hct because of angina from coronary artery disease should note an improvement of symptoms within a few weeks. Better exercise capacity is noted with each rise in Hct. In Table 2 are a few simple guidelines that will assure the benefits of a higher Hct while reducing the risks of too rapid a rise. I have found that a reticulocyte count is useful in the early stages of treatment in gauging individual sensitivity to r-HuEPO as well as detecting problems that were not previously diagnosed (Table 3).

Patient response to r-HuEPO is variable and seems unrelated to patient weight. In addition, in the United States a reimbursement cap of $40 per treatment has limited the use of r-HuEPO to a maximum of 4000 units per patient, encouraging dosing in the range of 2000 to 4000 units per patient rather than in units per kilogram. This method of dosing may direct therapy towards subcutaneous administration which may be more effective than IV use at the same dose [11], Before treating one should make sure that:

1. There is no active bleeding or hemolysis that might be masked.
2. Iron stores are repleted (% saturation, ferritin).
3. There are no other treatable causes of anemia.

In summary, r-HuEPO is a marvelous therapy leading to improvements in the quality of life of dialysis patients. To be determined is the ability of r-HuEPO to lengthen life. The obvious benefits of r-HuEPO must not be allowed to mask other risks to the dialysis patient-namely, those of inadequate dialysis. Careful medical application of this hormone should provide all of the benefits with none of the risks.

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