Does Parathyroid Hormone Affect Erythropoietin Therapy in Dialysis Patients?

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Key Words

Hyperparathyroidism • Anemia • Hemodialysis •
Peritoneal dialysis • Recombinant human erythropoietin

Abstract

Objective: The objective of this study was to assess the response to recombinant human erythropoietin (rHuEPO) during treatment of anemia in dialysis patients with hyperparathyroidism. **Subjects and Methods:** A total of 118 patients with stage 5 renal failure on dialysis therapy were selected for this study. Anemia was treated with rHuEPO. Laboratory data for each patient included intact parathyroid hormone (iPTH), hemoglobin (Hb), hematocrit (Hct), blood urea nitrogen, serum creatinine, calcium, phosphate, and alkaline phosphatase. Patients with iPTH >32 pmol/l were considered hyperparathyroid. Erythropoietin resistance index (ERI) was expressed as the ratio of weekly rHuEPO dose/Hct level. **Results:** Of the 118 patients, 83 (70.3%) were on hemodialysis (HD) and 35 (29.7%) were on continuous ambulatory peritoneal dialysis (CAPD). Sixty-three patients (64.3%) with iPTH >32 pmol/l had Hb <11 g/dl, while 34 (54.8%) with iPTH <32 had Hb >11 g/dl ($p = .04$). Thirty-three (56%) patients with iPTH >32 pmol/l had hemocrit <33%, while 38 (61.3%) with iPTH <32 had hemocrit <33% ($p = 0.4$). The median value of weekly rHuEPO dose in HD patients (12,000 units) was significantly higher in comparison with CAPD patients (6,000

units; $p < 0.0001$). ERI was significantly higher in HD than CAPD patients with iPTH <16 pmol/l ($p = 0.002$) as well as with patients with 16–32 pmol/l ($p = 0.012$). **Conclusions:** CAPD patients showed a reduced requirement for rHuEPO and better control of anemia compared with HD patients. ERI was also lower in CAPD than in HD patients. Hyperparathyroidism is a parameter predictive of rHuEPO hyporesponsiveness in dialysis patients. Copyright © 2007 S. Karger AG, Basel

Introduction

Anemia is a common concomitant disorder in dialysis patients. Improving the quality of life in these patients has been achieved by the use of recombinant human erythropoietin (rHuEPO), which became routine in the 1980s [1]. However, factors contributing to the degree of refractory anemia or so-called 'erythropoietin hyporesponsiveness' in dialysis patients are not well understood. Functional iron deficiency, blood loss, secondary hyperparathyroidism, aluminum toxicity, interaction with other drugs, infection and inflammatory conditions have been considered as predictors of poor response to erythropoietin treatment of anemia [2–5]. Secondary hyperparathyroidism is known to induce bone marrow fibrosis, impaired erythropoiesis [6] and inhibition of endog-

Table 1. Demographic features of studied patients

Patients	HD	CAPD	p value
Number	83	35	
Age, years			
Range	15 – 79	23 – 80	0.153 ^a
Mean $\pm$ SD	51.5 $\pm$ 15.2	55.8 $\pm$ 13.3	
Gender			
Male	30 (36.1%)	20 (57.1%)	0.029 ^b
Female	53 (63.9%)	15 (42.9%)	
Time on dialysis, months			
Range	4.0 – 217.0	4.0 – 91.8	0.004 ^a
Mean $\pm$ SD	32.1 $\pm$ 2.4	19.2 $\pm$ 2.1	
Renal disease			
Diabetic	20 (24.1%)	11 (31.4%)	0.779 ^b
Chronic GN	20 (24.1%)	11 (31.4%)	
Chronic IN	16 (19.3%)	5 (14.3%)	
Hypertension	10 (12%)	3 (8.6%)	
Others	4 (4.8%)	1 (2.9%)	

HD = Hemodialysis; CAPD = continuous ambulatory peritoneal dialysis; GN = glomerulonephritis; IN = interstitial nephritis.

^a Nonparametric Mann-Whitney test.

^b χ^2 test.

enous production of erythropoietin [7]. The impact of intact parathyroid hormone (iPTH) on the responsiveness to rHuEPO in dialysis patients is still not well understood. The purpose of this study was to assess the response to rHuEPO during treatment of anemia in dialysis patients with hyperparathyroidism.

Subjects and Methods

Patients who had been on renal replacement therapy for at least 6 months were selected for this study. All patients on hemodialysis (HD) were receiving three sessions a week utilizing hollow fiber dialyzers (regenerated cellulose or polysulfone). Patients on continuous ambulatory peritoneal dialysis (CAPD) were using the double bag system. All patients were on a stable rHuEPO dose, hemoglobin (Hb) level and medications for at least 3 months before the study. Medications included intravenous rHuEPO (epoetin beta), alfacalcidol capsules 0.25–0.5 μ g/day orally or in pulse therapy 2–8 μ g/week, phosphate binders, antihypertensive drugs and vitamins. Patients with Hb concentration <11 g/dl and hematocrit (Hct) <33% were considered anemic as recommended by Kidney-Dialysis Outcomes Quality Initiative: K/DOQI Clinical Practice Guidelines [8].

Laboratory data for each patient included Hb, Hct, blood urea nitrogen, serum creatinine, serum calcium corrected for the level of serum albumin, serum phosphorus and alkaline phosphatase

(ALP). All data were expressed as the mean value of 3 readings. Patients with iPTH 32 pmol/l or more were considered to have hyperparathyroidism as recommended by K/DOQI Clinical Practice Guidelines [9]. Erythropoietin resistance index (ERI) was expressed as the ratio of weekly rHuEPO dose/Hct level. The statistical package for social sciences was used for data processing using cut-off level for significance as $p \leq 0.05$. Various descriptive statistics were used to define the median of variables. Non-parametric Mann-Whitney test was used to compare the medians of undependable variables. χ^2 test and Fisher's exact test were used to define the association between independent variables, as appropriate. Spearman rank correlation was used to define the p value and correlation coefficient of independent variables.

Results

The demographic characteristics of the patients are given in table 1. There was no significant difference in age between HD and peritoneal dialysis patients. The time on dialysis was significantly longer for HD (4–217 months) than CAPD (4–91.8 months) patients ($p = 0.004$). Diabetic nephropathy and chronic glomerulonephritis were the common causes of stage 5 renal disease in all studied patients.

Laboratory parameters of the patients are given in table 2. Intact iPTH was higher in HD (33 pmol/l) than in peritoneal dialysis (24 pmol/l) patients. The difference, however, was not significant ($p = 0.17$). Also, Hb, Hct, ferritin, calcium, phosphate and ALP levels were not significantly different between HD and CAPD patients ($p > 0.05$). However, erythropoietin dose per week was significantly lower in CAPD than in HD ($p < 0.0001$). ERI in peritoneal dialysis was significantly lower than in HD patients ($p < 0.004$).

The relationship between rHuEPO resistance index and iPTH levels in HD and CAPD is shown in figure 1. rHuEPO resistance index was significantly higher in HD than CAPD patients with iPTH <16 pmol/l ($p = 0.002$) as well as patients with 16–32 pmol/l ($p = 0.012$). There was no significant difference between HD and CAPD patients with iPTH higher than 32 pmol/l.

Hb and Hct levels at iPTH level < and >32 pmol/l for all the patients are shown in table 3. With Hb level <11 g/dl, more patients (36) had iPTH level >32 than when the level was <11 g/dl (28 patients); the difference was statistically significant ($p = 0.04$). Also, with Hct level <33% more patients (33) had iPTH level >32 than when the level was >33%; the difference was also statistically significant ($p = 0.044$).

Table 2. Laboratory parameters

	HD			CAPD			p value ^a
	median	25th percentile	75th percentile	median	25th percentile	75th percentile	
iPTH, pmol/l	33	17.9	64.0	24	8.5	53.4	0.168
Hb, g/dl	11	10.30	11.8	11	10.1	12.0	0.777
Hct, %	32	30.0	35.2	32	29.9	35.0	0.637
Ferritin, ng/ml	130	71	236	194	123	279	0.035
rHuEPO dose, units/week	12,000	6,000	1,200	6,000	4,000	8,000	<0.0001
ERI	317.46	193.54	467.28	192.9	125.0	280.7	0.001
Corrected Ca, mmol/l	2.46	2.32	2.56	2.58	2.53	2.74	0.461
Phosphate, mmol/l	1.81	1.42	2.2	1.52	1.20	2.04	0.089
Albumin, g/l	32	30	34	28	23	33	<0.0001
ALP, IU/l	78.0	66.0	106.0	85.0	125	280	0.337

iPTH = Intact parathyroid hormone; rHuEPO = recombinant human erythropoietin; ALP = alkaline phosphatase; ERI = recombinant human erythropoietin resistance index.

^aNonparametric Mann-Whitney test.

Fig. 1. Relation between rHuEPO resistance index and iPTH levels in HD and CAPD.

Discussion

Conflicting data have been reported regarding the role of parathyroid hormone in conditioning the response to rHuEPO in dialysis patients [4, 6, 7]. Few studies [10] have compared the responsiveness of erythropoietin

Table 3. Hb concentration at iPTH levels <32 and >32 pmol/l for all the patients

	iPTH, pmol/l		p value ^a
	<32	>32	
Hb			
<11 g/dl	28 (45.2%)	36 (64.3%)	0.0433
>11 g/dl	34 (54.8%)	20 (35.7%)	
Hct			
<33%	24 (38.7%)	33 (56%)	0.0420
>33%	38 (61.3)	23 (40%)	

iPTH = Intact parathyroid hormone.

^aFisher's exact test.

therapy in patients with hyperparathyroidism and parathyroid hormone below the recommended level. Severe hyperparathyroidism is one of the factors involved in erythropoietin response [6]. Theoretically, medical and/or surgical suppression of iPTH over secretion should have a similar effect on anemia detected in dialysis patients. Some authors reported a better response in patients with relative hypoparathyroidism [10]. Yet, others found no relationship between hyperparathyroidism and poor response to erythropoietin [11, 12]. A higher requirement for rHuEPO in patients with elevated iPTH

has been reported in HD patients. In peritoneal dialysis patients, the rHuEPO requirement is reduced, and there is less frequent administration of rHuEPO than in HD patients [13]. Our study has consistently shown that Hb was significantly better in patients with iPTH levels <32 pmol/l. Moreover the requirement for rHuEPO was less in CAPD than HD patients.

Considerable improvement of anemia has been noted in patients commenced on or switched to CAPD [14, 15]. Generally, anemia in CAPD patients seems to be less severe than in HD patients, and a greater proportion of patients on CAPD achieve normal Hct than do patients on HD. The underlying mechanisms may include such various factors as reduced blood (and iron) loss and improved EPO production. Better clearance of middle molecule substance in CAPD [16] than with standard HD could in part explain the reduced requirement of rHuEPO in this dialysis modality. Inhibitors of aminolevulinate dehydrase, an enzyme involved in Hb metabolism [17], and albumin-bound furancarboxylic acid, an inhibitor of erythropoiesis [18], are possibly removed more efficiently by peritoneal dialysis.

An important finding of our study was the strong association between indices of refractory anemia in the form of rHuEPO hyporesponsiveness and high levels (>32 pmol/l) of parathyroid hormone. In this study, the overall ERI was significantly lower in CAPD than in HD

when parathyroid hormone was <32 pmol/l. ERI, however, was not significantly different in HD compared to CAPD when iPTH was >32 pmol/l.

Better responsiveness was reported in patients on HD with relative hypoparathyroidism [10, 19]. A recent study has shown that higher serum calcium and phosphate levels are independently associated with better anemia control [20]. Inhibition of erythropoietic progenitors and changes in tissue sensitivity to erythropoietin and parathyroid hormone has been proposed to have a direct negative impact on the responsiveness to erythropoietin [21]. Additionally plasma level of erythropoietin dramatically increases 1–2 weeks after surgical parathyroidectomy [22].

Conclusion

CAPD patients showed a reduced rHuEPO requirement than HD patients. Treatment of anemia with rHuEPO is more easily achieved in CAPD than HD patients. ERI is lower in CAPD than in HD patients. Hyperparathyroidism is a predictor parameter of rHuEPO hyporesponsiveness in dialysis patients. We advocate a combined therapeutic approach, that is, treating both anemia and overproduction of parathyroid hormone.

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