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PHARMACOKINETICS OF RECOMBINANT ERYTHROPOIETIN AND RED CELL METABOLISM IN HAEMODIALYSIS PATIENTS

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ABSTRACT

The pharmacokinetics of recombinant human erythropoietin (rHuEpo) administered intravenously has been investigated in a group of five patients with chronic renal failure who were dialysis-dependent. The half-life of circulating erythropoietin decreased from 7.9±0.4 hr (mean ±SD) at the beginning of treatment to 6.2±0.6 hr after 6 weeks and 5.4±0.9 hr after 4 months of treatment. In spite of the sustained increase in haemoglobin neither the red cell 2,3,-diphosphoglycerate (2,3-DPG) nor the P50 decreased from the pretreatment values. The mechanism which governs the rise in 2,3-diphosphoglycerate in chronic renal failure is different from the adaptive mechanism which operates in other types of anaemia.

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Key Words: Recombinant Erythropoietin, Red Cell Metabolism, Chronic Renal Failure

INTRODUCTION

The anaemia of chronic renal failure (CRF) is caused by a relative deficiency of erythropoietin (Epo), the principal regulator of red cell mass. Epo is a 30,400 Dalton acidic glycoprotein normally secreted by the kidney and has been purified to apparent homogeneity.[1] The human Epo gene has been cloned[2,3] and the recombinant DNA-derived hormone used to treat the anaemia of chronic renal failure.[4,5] Initial clinical trials of intravenous rHuEpo have been encouraging, although large doses have been required. There is little information available about the half-life of administered Epo.

In chronic renal failure red cell 2,3-diphosphoglycerate (2,3-DPG) is increased[6] but in contrast to other types of anaemia the rise in 2,3-DPG is not always associated with an increase in P50.[7,8,9]

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The aims of the present investigation were to determine the effect of continued intravenous recombinant human erythropoietin (rHuEpo) therapy upon the half life of the rHuEpo and upon the red cell 2,3-DPG and P50 values.

SUBJECTS AND METHODS

Five patients with end-stage renal disease maintained on twice-weekly haemodialysis were treated with rHuEpo (Ortho-Cilag, Schaffhausen, Switzerland). The treatment, which lasted for four months, consisted of 50 U/kg rHuEpo thrice weekly, increasing by 25 U/kg every four weeks to a maximum of 100 U/kg. One patient received a kidney transplant after 3 months of treatment with rHuEpo. The control subject was a healthy adult male, who was venesected on each occasion when patients were venesected.

Haemoglobin, renal chemistry values, serum erythropoietin, 2,3-DPG, and P50 were measured before treatment with rHuEpo and after treatment for 6 weeks and

Table 1: Erythropoietin half-life, haemoglobin, 2,3-DPG and P50 values over the treatment period.

	First dose (n= 5)	Six Weeks (n= 5)	Four Months (n= 4)	Controls (n= 12)
Erythropoietin half-life (hour)	7.9±0.4	6.2±0.6**	5.4±0.9*	
Haemoglobin (g/l)	61.8±10.0	84.6±10.4*	109.6±7.1**	151.0±5.0
2,3-diphospho-glycerate (µmol/gHb)	18.9±4.6*	21.0±2.9	18.7±3.0*	12.5±1.3
P50 (mmHg)	25.1±2.3	27.1±2.2	27.6±1.3	26.7±1.8

Values given are mean ±1SD

*P<0.01

** P<0.001

+1 patient was transplanted after 3 months treatment with rHuEpo

4 months. The half-life of rHuEpo was estimated after the first dose, and after treatment for 6 weeks and 4 months. Following injection of rHuEpo blood samples were removed at 5 min and thereafter at two hourly intervals for 12 hr for estimation of the half-life of rHuEpo by the method of Emmanouel et al.[10]

Haemoglobin and renal chemistry values were measured by standard laboratory procedures. Serum erythropoietin was determined by radioimmunoassay,[11] 2,3-DPG enzymatically[12] and the P50 was calculated from the haemoglobin-oxygen dissociation curve (ODC) obtained using the Hem-O-Scan®, in accordance with the procedure recommended by the manufacturers (Travenol Laboratories, Silver Spring, MD). Statistical analysis was performed by the Student-t test.

RESULTS

Haemoglobin levels increased in all five patients treated with rHuEpo. Before treatment the mean haemoglobin value was 61.8 g/l and this increased to 84.6 g/l after treatment for 6 weeks and to 109.6 g/l after 4 months (see Table I).

The mean half-life of Epo was 7.9 hr after the first dose, and decreased to 5.4 hr after therapy for 4 months (see Table I). Throughout the study period there was no detectable change in serum Epo levels prior to injection.

Patient red cell 2,3-DPG levels were higher than normal controls but did not alter significantly during the study period. Similarly, patient P50 values remained unchanged (Table I). Pre-dialysis renal chemistry values did not change significantly during treatment period and in particular there was no alteration in serum inorganic phosphate levels.

DISCUSSION

Recombinant human erythropoietin was an effective treatment for the anaemia of chronic renal failure for all five patients. No complications were observed, except in one patient who required intensification of treatment for hypertension. Side effects of hypertension and thrombosis of vascular access have been reported in other studies.[4,5] Currently the widespread use of erythropoietin is precluded by concern about possible side-effects and its economic cost.

Although the most efficient route of administration has yet to be determined, intravenous rHuEpo has a shorter half-life than subcutaneous rHuEpo.[13] The observation that the half-life of intravenous rHuEpo decreases with continued treatment is of interest. It suggests that the clearance of Epo changes with prolonged treatment. If the half-life of Epo does decrease with continuing intravenous therapy it may partly explain the requirement for high therapeutic dosage levels, although caution is required in the interpretation of data from this small group of patients. The current economic cost of rHuEpo treatment is a limiting factor in its widespread application. Subcutaneous injection may well prove to be the optimal route of administration of rHuEpo to achieve therapeutic effects (at lower dosage) by virtue of its reported longer half-life.[13]

One of the compensatory mechanisms for the decreased oxygen-carrying capacity of blood in anaemia is the right-shift of the ODC which results in a rise in P50.[14,15] A right-shift of the ODC in anaemia is generally associated with an increase in the red cell metabolite 2,3-DPG.

In anaemia patients there is an inverse relationship between P50 and haemoglobin.[14,16] Studies undertaken with patients suffering from the anaemia of chronic renal failure have shown divergent results. Mitchell and Pegrum[7] found

significantly higher P50 values in patients with CRF than in normal subjects. In contrast Humpeler et al.[8] found lower P50 values in a group of CRF patients than normal subjects. Bocker et al.[9] found no significant differences in P50 between 16 patients with CRF and 12 normal subjects. Our data is in agreement with Bocker et al. who reported no change in P50 in their CRF group after therapy with rHuEpo for 50-101 days in spite of a significant rise in Hb.

A right-shift of the ODC in anaemia is generally associated with an increase in the red cell 2,3-DPG. In this investigation the 2,3-DPG levels in the CRF patients were significantly higher than in the control subjects, but the P50 values for the two groups were similar. This suggests a weaker correlation between P50 and 2,3-DPG in CRF than in other types of anaemia. Our findings are in agreement with those of Lichtman and Miller[6] who demonstrated that hyperphosphataemia, a common finding in CRF, causes a rise in red cell 2,3-DPG.

Correction of anaemia would normally be expected to cause a decrease in 2,3-DPG. In our study there was no significant decrease in 2,3-DPG despite the increase in mean Hb from 61.8 to 109.6 g/dl overthe 4 month period of treatment. Bocker et al. even noted a small increase of 2,3-DPG after treatment with rHuEpo which produced a rise in Hb from 73 to 113 g/l.

The stability of P50 and 2,3-DPG values despite a significant and substantial increase in haemoglobin suggests that the normal compensatory mechanism is perturbed in CRF.

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