SUSTAINED NEGATIVE FEEDBACK BETWEEN HAEMATOCRIT AND SERUM ERYTHROPOIETIN CONCENTRATION IN END-STAGE RENAL FAILURE

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Summary

In a longitudinal study the individual values of serum erythropoietin (SEp) in end-stage renal failure were investigated in 15 patients. SEp was determined by use of the foetal mouse liver cell assay on three occasions: (A) 2–6 months before the onset of RDT, (B) on day of first dialysis, and (C) 2–6 months following the onset of RDT. In every patient SEp increased from (A) to (B), and decreased again from (B) to (C). Changes of haematocrit were exactly opposite to changes of SEp. The results demonstrate that even in the terminal stage of chronic renal failure erythropoietin production is stimulated or suppressed in response to variations in the degree of anaemia.

Introduction

Erythropoietin (Ep) is responsible for the day to day regulation of erythropoiesis, and decreased tissue oxygenation is usually answered by an increase of Ep production. Alexanian demonstrated a negative correlation between haematocrit (Hct) and serum erythropoietin (SEp) concentration in a group of patients with various types of anaemia of other than renal origin [1]. Napier and co-workers found the same correlation in anaemic patients without renal disease using the foetal mouse liver cell technique [2].

SEp levels in patients with renal disease are usually found to be inadequately elevated in relation to the degree of anaemia [3,4], and Erslev and Wallner found no correlation between Hct and SEp in patients with renal anaemia [5]. Last year in Helsinki, we reported a large group of patients with end-stage renal failure undergoing haemodialysis treatment, of which one half had a positive correlation between Hct and SEp, whereas in the other half the correlation was inverse. The latter behaviour was interpreted by us as an indication of an intact feedback mechanism in a surprisingly large number of uraemic patients [6].

To obtain further evidence for this assumption we investigated in the present study whether in individual patients with end-stage renal failure a sustained negative feedback between Hct and SEp concentration also exists.
Patients and Method

In a longitudinal study we followed 15 patients with terminal renal failure, 8 males, and 7 females, aged from 30–63 years. The diagnoses of underlying renal disease were: glomerulonephritis (5), interstitial nephritis (5), polycystic kidney disease (4), and nephrosclerosis (1). In addition, SEp levels of 59 healthy controls were measured for comparison.

Blood samples for Hct and Ep measurements were taken from each patient on three different occasions, characterised by different degrees of renal anaemia: (A) 2–6 months before onset of regular dialysis treatment, (B) on day of first dialysis immediately before the start of treatment, and (C) 2–6 months after onset of regular dialysis treatment (again before the start of dialysis).

SEp determinations were performed by use of the foetal mouse liver culture as described by Wardle et al [7], and Dunn et al [8]. In principle, haemopoietic active liver cells from 14 day old mouse foetuses incorporate radioactive iron in proportion to the Ep concentration in the culture. The sensitivity of the method goes down to 0.5 mU/ml final dilution, corresponding to 5 mU/ml test serum, when a maximal test serum portion of 10% in the culture is used. The coefficient of variation determined in 30 double measurements was 14%, the mean limits of confidence determined in 59 measurements were 83 and 119% of the mean potency, and the index of precision also determined in 59 samples ranged from 0.04–0.35 with a mean of 0.13.

Results

Mean Hct and mean SEp levels derived from the measurements on the three indicated occasions are shown in Figure 1 together with the corresponding mean values of normal controls. Two to six months before start of regular dialysis treatment mean Hct of 27.3 ± 1.1 (SD) % was accompanied by a mean SEp concentration of 200 ± 42 mU/ml. On the day of first dialysis mean Hct had dropped to 22.7 ± 0.9 %, and mean SEp concentration had increased to 596 ± 91 mU/ml. Two to six months following the onset of regular dialysis treatment mean Hct had increased to 27.0 ± 0.9 %, whereas mean SEp concentration had decreased to 309 ± 37 mU/ml. Mean Hct values and mean SEp levels were significantly different (P < 0.001) when results of the first and second, and second and third measurements were compared. On all three occasions mean Hct values and mean SEp concentrations were significantly different from normal controls (P < 0.01). In general, lower Hct values were accompanied by higher SEp concentrations and vice versa. This relationship became more evident when the course of Hct and SEp in individual patients was observed. Figure 2 shows that Hct decreases during the last months of the predialysis phase and increases after 2–6 months of regular dialysis treatment in every patient. As demonstrated in Figure 3 individual SEp concentrations behave in the opposite way. Again, Hct values and SEp levels are significantly different when first and second, and second and third measurements are compared using the paired t-test (P < 0.001).
Figure 1. Serum erythropoietin (SEp) concentration and hematocrit (Hct) during the development of terminal renal failure and following the onset of dialysis treatment compared with normal control values.

Discussion

The results confirm our recent finding [6] of elevated SEp levels in patients with renal anaemia, and are in good agreement with data obtained in a small number of uraemic patients by immunologic Ep assays [9,10]. The failure of earlier studies [3,4] to demonstrate elevated SEp concentrations in patients with chronic renal failure may be explained by underestimation of Ep in uraemic serum by the polycythaemic mouse assay used [10].

The data clearly demonstrate that there is a considerable capacity to increase Ep production in response to hypoxia when anaemia becomes more severe with progression of the uraemic state. The reversibility of this regulatory
Figure 2. Haematocrit (Hct) during the development of terminal renal failure and following the onset of dialysis treatment
increase of SEp when anaemia improves following the onset of dialysis treatment shows that in chronic renal failure the known negative feedback between Hct and SEp is still intact. However, one has to assume that in regard to absolute SEp concentrations this feedback mechanism operates at a lower level than in anaemic patients without renal disease. Although other factors such as pulmonary fluid overload, cardiac insufficiency, red cell 2,3 DPG concentration [11], and acidosis [4] may influence oxygen delivery to oxygen-sensitive
receptors in chronic renal failure, the peripheral haemoglobin concentration appears to play the most important role in tissue oxygenation in uraemic patients.

References


Open Discussion

NAIK (Portsmouth) We use the same method to measure erythropoietin levels in uraemic patients, based on Napier's method. We too found that erythropoietin levels were in the normal range in these patients but the levels were low for the degree of anaemia that these patients had. Did you find inhibitors in the serum and did they influence your assay?

ERBES We did not find inhibitors. On the day of maximum intoxication, namely, on day of first dialysis we found the highest erythropoietin activity.

ZAZGORNITK (Vienna) What do you think about inhibiting factor of erythropoietin? Secondly, did you compare patients dialysed with cuprophan and patients dialysed by the Rhone Poulenc, for example? Have you found any difference between the haematocrit and erythropoietin levels?

ERBES No. We have not found any difference, nor any inhibiting factors.

KOGAK (Istanbul) Have you any experience with polycystic disease?

ERBES We measured patients with polycystic kidney disease and found their erythropoietin levels in the normal range. In patients with polycystaemia we found the erythropoietin levels even lower.

KANIS (Oxford) It seems to me that possibly the crucial part of your study is the finding of rather high erythropoietin levels on the first day of dialysis and without that finding you would not have found inverse correlations. Now how sure are you that at that time you are in a steady state situation and have you looked at erythropoietin levels on the day before starting the first or perhaps one or two weeks after starting haemodialysis? Are they still high at that time?
ERBES Yes, they are. In some patients we measured also a few days before and after onset of RDT, and erythropoietin levels were at the same level.