IS THERE A DISSOCIATION OF ERYTHROPOIETIC PROLIFERATION AND SERUM ERYTHROPOIETIN LEVELS IN RENAL FAILURE PATIENTS ON LONGTERM HAEMODIALYSIS TREATMENT?

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Summary

The demonstration of a sustained erythropoietin (EP) — haematocrit (HCT) feedback mechanism would underline the importance of EP as a stimulant agent for the erythropoietic proliferation (EPRO) in chronic uraemia. Hypertransfusion showed a significant suppression of EPRO without a concomitant suppression of the pretransfusional immunodetectable (id) serum EP levels. We conclude that idEP is not the major direct mediator of EPRO in short term regulatory mechanisms in the anaemia of uraemia.

Introduction

Erythropoietin has, among other functions, a stimulating effect on the proliferative activity of red cell precursors (EPRO). A high HCT suppresses the production of EP and consequently the EPRO.

As patients with terminal renal failure (RFPs) often suffer from hypoproliferative anaemia, a shortcoming within the EP-HCT feedback control might be suspected.

In a recent report [1] we presented evidence for a relative deficit of immunodetectable (id) EP in RFPs. To study the significance of idEP levels for EPRO in RFPs we tested the response of EPRO and EP to a strong stimulant and a subsequent suppressive impulse.

Materials and methods

Nineteen patients on longterm haemodialysis treatment (LHT) were run on low HCT levels for one week in order to develop a strong stimulus to their erythropoiesis. Twelve patients were then transfused with 500ml washed concentrated erythrocytes (ERY), seven patients received 2 × 500ml ERY within two days. Clinical data are summarised in Table I. None of the patients had any transfusions
TABLE I. Pretransfusion data of the investigated patients (means ± SD)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppression tests</td>
<td>Number</td>
<td>25</td>
</tr>
<tr>
<td>Haematocrit (HCT)</td>
<td>L/L</td>
<td>0.16 ± 0.02</td>
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<tr>
<td>Haemoglobin (Hb)</td>
<td>g/dl</td>
<td>4.9 ± 0.7</td>
</tr>
<tr>
<td>Serum iron (SI)</td>
<td>µg/dl</td>
<td>143.2 ± 86.4</td>
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<tr>
<td>Serum creatinine</td>
<td>mg/dl</td>
<td>7.8 ± 1.9</td>
</tr>
<tr>
<td>Reticulocyte count (RC)*</td>
<td>%</td>
<td>31.9 ± 19.2</td>
</tr>
<tr>
<td>Immuno-detectable erythropoietin (idEP)†</td>
<td>MIU/ml</td>
<td>20.8 ± 9.9</td>
</tr>
</tbody>
</table>

* Reticulocyte count corrected for anaemia: reticulocytes (%) × patient’s HCT(L/L) divided by 0.45
† Milli-immunochemical units; normal range: 7–36MIU/ml

or other anti-anaemic medications for at least three months prior to the study. The immuno-detectable serum EP was determined by means of the haemagglutination-inhibition assay [2].

Results

Table I shows the pretransfusion (PRE) data of the patients. A very low HCT was associated with normal average values of idEP titres in more than 80% of the determinations. Figure 1 outlines the post-transfusional (POST) course of the HCT after a 500ml transfusion of ERY. The percentages of the maximum POST elevations ranged from 123–183% of the PRE levels. The correlation coefficient of the PRE HCT and the maximum POST HCT was r = 0.7302, suggesting that the PRE HCT could not serve as a very reliable indicator of the severity of the erythropoietic stimulus.

The Post idEP levels (Figure 2a) between two hours and 20 days after 500ml ERY did not deviate from the PRE levels.

In order to test the sensitivity of a possibly operative feedback mechanism between the HCT and the idEP, some RFPs received 2 × 500ml ERY within two days. The PRE HCT values averaged 15.2 ± 2.6%, the POST HCT values were raised to 230 ± 64% of the PRE HCT levels. Despite these intense PRE stimulant and POST suppressive impacts on EPRO we could not discern any significant alterations of the idEP levels (Figure 2b).

Although the idEP levels remained unaffected by either 500 or 1,000ml of ERY, there was a profound reduction of the POST reticulocyte count (RC) (Figure 3).

In addition, we recognised a relationship between the kinetics of the reactive RC depression and the duration of chronic intermittent haemodialysis treatment (CHT). The longer the patient had been on CHT the more prolonged was the suppressive effect of the ERY on his EPRO.
Figure 1. Per cent deviation from pretransfusion levels of the haematocrit following transfusions (arrow) of 500ml erythrocytes. 100% = pretransfusion level. Curves of nine representative patients

Figure 2. idEP levels before and after transfusions of 500ml (A, one arrow) and 2 × 500ml (B, two arrows) erythrocytes. Shaded areas = normal ranges for healthy subjects
Discussion


The contribution of a deficit of EP to the development of the anaemia in RFPs could best be elucidated if the HCT-EP feedback mechanism [9, 10] was demonstrated to be operative in chronic renal failure (CRF).

As a measure of the EP activity we determined the idEP levels [2] in uraemic sera. The RC represented our measure of the EPRO. Others [11] have shown a correlation between a given transfusion and the POST percentage of normoblasts in RFPs.

In our study, a low HCT of 16 ± 2% was associated with a high RC of 32 ± 19% (normal 5–15%). The transfusions dropped the RC to 10 to 30% of the PRE levels. Hence, EPRO was well influenced by the peripheral HCT. However, the idEP titres remained unaffected as well after 500 as after 1,000ml ERY. Therefore, we conclude that idEP as determined with the available haemagglutination-inhibition assay was not the compound to modulate EPRO in CRF during short term regulatory mechanisms. The idEP levels did not respond to ERY-induced suppression of EPRO lasting from four days to five weeks (Figure 3). On the other hand, idEP titres seemed to bear some relevance in longterm regulatory mechanisms to maintain a required minimum HCT during LHT of up to seven years [1]. Substances [11] other than idEP seem to play a part in the postulated [11] persistent humoral regulation mechanism between the HCT and EPRO in CRF.
References

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Open Discussion

PARSONS (London) I was interested to see how high your reticulocyte counts were in some of your patients and I wonder if you had excluded a chronic haemolytic anaemia. What were their red cell survival times? Did they have splenomegaly and what were their haptoglobin levels for instance?

WALLE We did not measure the erythrocyte survival time so I cannot tell you anything about the true turnover rate of the erythrocytes.

JONTOFSOHN (Freiburg) What kind of quality control of erythropoietin measurement have you done? Essess found poor correlation between immunoassay and bio-assay.

WALLE I know about these problems and we have decided to use other test systems, for example the polycythaemic mouse assay and the radioimmunoassay developed by Garcia.

LEVI (Israel) Did you measure PTH in your study?

WALLE No.

HARROW (Salt Lake City) Have you made any correlation between either male or female sex or the amount of male hormone levels in regard to response?

WALLE No, because we felt the number of patients too small for statistical analysis.