ARE ERYTHROPOIETIN LEVELS IN URAEMIC PATIENTS ON HAEMODIALYSIS DEPENDENT ON THE KIDNEY DISEASE AND THE DURATION OF HAEMODIALYSIS TREATMENT?

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Summary

Determinations of immuno-detectable Erythropoietin (idEP), haematocrit (Hct), reticulocyte counts (RC) and serum iron (SI) in uraemic patients with different kidney diseases (KD) and various lengths of chronic haemodialysis treatment (HDT) revealed firstly that all patients had normal idEP, except for analgesic nephropathies who had significantly higher idEP levels; secondly that over six years of haemodialysis idEP increased by about 40% but without concomitant Hct improvement and thirdly that there were no clear interdependencies between Hct, SI, RC and idEP in uraemic patients. In conclusion, inhibitors of erythropoiesis seem to be a major pathogenetic factor in renal anaemia besides a relative deficit in idEP.

Introduction

The pathogenetic significance of Erythropoietin (EP) in the anaemia of chronic renal failure (RF) is not thoroughly understood. Relative or absolute lack of EP [1-4] as well as high levels of EP [5,6] were reported for RF-patients (conditions with low serum iron were excluded in those studies). These conflicting results might be due to several experimental conditions, namely different methods of assaying EP, different kidney diseases underlying the RF, and different duration of RF at the time the determinations were performed. Hence, the present study was designed to test whether the EP levels in RF were dependent on the underlying kidney disease (KD) and on the duration of chronic intermittent haemodialysis treatment (HDT).

Patients and Methods

In 36 (20 f, 16 m) patients with RF of different aetiologies (Table I) and various durations of HDT (Table I) the following set of parameters was investigated:
TABLE I. Numbers (No) of patients with different kidney diseases (KD) and different time periods of haemodialysis treatment (THT, periods of treatment indicated in months)

<table>
<thead>
<tr>
<th>KD</th>
<th>No</th>
<th>THT (months)</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGN (chronic Glomerulonephritis)</td>
<td>9</td>
<td>0–10</td>
<td>17</td>
</tr>
<tr>
<td>cPN (chronic Pyelonephritis)</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aGN (acute Glomerulonephritis)</td>
<td>3</td>
<td>15–26</td>
<td>12</td>
</tr>
<tr>
<td>ciN (algesic Nephropathy)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyst (polycystic KD)</td>
<td>4</td>
<td>34–40</td>
<td>10</td>
</tr>
<tr>
<td>diab (diabetic Glomerulosclerosis)</td>
<td>4</td>
<td>44–49</td>
<td>9</td>
</tr>
<tr>
<td>Nek (bilateral Nephrectomy)</td>
<td>2</td>
<td>51–75</td>
<td>6</td>
</tr>
<tr>
<td>amyI (amyloid Nephrosis)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serum Erythropoietin (immuno-detectable EP = idEP by the method of Lange [7]), reticulocyte counts (RC, two persons each determined the RC of 2000 red cells from one venous blood sample), serum iron (SI, [8]), and the haematocrit (Hct). A total of 54 determinations of this set was performed. The dialysis regimen was a four hours thrice weekly intermittent haemodialysis programme.

Results

In general, the idEP values for all the patients were within normal limits, i.e. 7–36MIU/ml. The idEP levels were subnormal, i.e. 5MIU/ml, or slightly increased, i.e. 38 MIU/ml in fewer than 20% of the determinations.

There were no correlations between the idEP, the Hct, the RC or the SI.

In individual cases, repeated determinations revealed idEP levels ranging from subnormal to slightly increased without concurrent changes of the other parameters.

The idEP levels were all within the same range in the different groups of KDS (Table II), except for the algesic nephropathies (ciN) with their significantly raised idEP values. In parallel, RC was highest and SI was lowest in cases of CIN.

During a period of 6 yr HDT there was a significant increase in idEP of 40% (Figure 1) but without concomitant improvement of the Hct, which varied irregularly between 16 and 26% with the maximum of 26% between the third and fourth year of HDT.

Discussion

Varying erythropoietic activity (EP–A) levels in the sera of RF—patients have been reported [7,9]. One of the possible explanations might be the variety of the underlying KDS. This argument would be in keeping with reports that some RF patients with polycystic KDS exhibited surprisingly high Hct values as compared with RF patients of other aetiology [10].

Another difficulty in elucidating the relationship between the haematological
TABLE II. Haematological parameters of the different groups of kidney diseases (KD).
(idEP = immuno-detectable Erythropoietin, Hct = haematocrit, RC = reticulocyte count
corrected for anaemia, Fe = serum iron)

<table>
<thead>
<tr>
<th>KD</th>
<th>idEP (MIU/ml)</th>
<th>Hct (l/l)</th>
<th>RC (°/o)</th>
<th>Fe (mg/dl)</th>
<th>No of determinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGN</td>
<td>11.9 ± 4.9</td>
<td>21 ± 4</td>
<td>6 ± 4</td>
<td>113 ± 63</td>
<td>n = 15</td>
</tr>
<tr>
<td>cPN</td>
<td>15.4 ± 8.8</td>
<td>18 ± 6</td>
<td>8 ± 5</td>
<td>120 ± 82</td>
<td>n = 15</td>
</tr>
<tr>
<td>aGN</td>
<td>7.3 ± 2.6</td>
<td>18 ± 5</td>
<td>3 ± 2</td>
<td>62 ± 8</td>
<td>n = 4</td>
</tr>
<tr>
<td>dIN</td>
<td>60.2 ± 20.2</td>
<td>17 ± 3</td>
<td>15 ± 5</td>
<td>29 ± 16</td>
<td>n = 6</td>
</tr>
<tr>
<td>cyst</td>
<td>13.0 ± 7.1</td>
<td>27 ± 2</td>
<td>10 ± 1</td>
<td>47 ± 15</td>
<td>n = 5</td>
</tr>
<tr>
<td>diab</td>
<td>18.1 ± 5.6</td>
<td>19 ± 5</td>
<td>10 ± 5</td>
<td>71 ± 30</td>
<td>n = 4</td>
</tr>
<tr>
<td>Nek</td>
<td>14.0 ± 4.8</td>
<td>16 ± 1</td>
<td>4 ± 3</td>
<td>63 ± 39</td>
<td>n = 2</td>
</tr>
<tr>
<td>amy1</td>
<td>14.1 ± 4.9</td>
<td>16 ± 2</td>
<td>6 ± 2</td>
<td>50 ± 7</td>
<td>n = 3</td>
</tr>
</tbody>
</table>

findings (Hct, EP–A) and the KDs arose from the variety of methods applied for the determinations of EP–A. This is a crucial problem because of the heterogeneity of erythropoietically active molecular substances and the simultaneous measurement of inhibitors to erythropoiesis using bioassays. For these reasons we used only one method throughout all the studies to determine the idEP in our RF patients.


In general, the idEP levels in this study were nearly all within the normal range indicating a relative deficit of idEP in relation to the degree of anaemia.

The results (Table II) lead to the conclusion that in all the aetiological groups of KDs the idEP levels were the same except for RF patients with analgesic nephropathy who exhibited significantly higher idEP levels. However, these cIN-patients had lower serum iron (SI) levels in spite of normal or high normal bone marrow iron stores. In earlier reports, low SI values were linked to high EP–A levels [12,13]. However, many of our other KD groups also had low SI values sometimes which were not associated with high idEP levels. Hence, low serum iron levels may not be the critical factor causing high idEP levels in cIN patients. In these patients the reticulocyte counts were raised above the average found in the other KD groups, possibly in response to their elevated idEP levels.

Chronically increased haemolysis in patients with analgesic nephropathy as an underlying cause for steadily stimulated erythropoiesis could not be proved by routine laboratory methods (determinations of the lactate-dehydrogenase isoenzymes and the plasma haemoglobin), and neither was occult blood loss found in the stools. However, ferrokinetic measurements were not performed. Another finding of this study was that HDT lasting 6 years was associated with an increase in idEP of about 40%, but there was no concomitant improvement in the Hct and/or the reticulocyte count during this period of time.

From these results it is concluded that the type of KD is not a factor in the pathogenesis of renal anaemia with respect to the production of idEP. The increased erythropoietic activity in cIN-patients (elevated idEP and RC) cannot
be explained without ferrokinetic measurements in analgesic nephropathy. The dissociation between the Hct and the idEP in long term HDT suggests that the accumulation of erythropoietic toxins during long term haemodialysis may be a major pathogenetic factor in chronic uraemic anaemia. Consequently, one therapeutic aim should be the elimination of inhibitors to red cell production rather than the administration of a drug ‘Erythropoietin’.

References

3 Essers, U (1972) Blut 24, 346
Open Discussion

DRÜEKE (Paris) What were the serum idEP levels in anephric patients? Your conclusion that exogenous erythropoietin might not be helpful in the treatment of anaemia in uraemic patients is in contradiction with a recent paper in Kidney International where it was shown that exogenously administered EP significantly reduced the severity of anaemia in anephric rats on peritoneal dialysis.

WALLE To the first question, we had two anephric patients who had just the same immunodetectable EP-level as all the other patients except those with chronic interstitial nephritis though there was no significant difference between them. To your second question I think that the increasing idEP levels during the 6 year period of haemodialysis may be a response to the accumulation of toxic cell-proliferation inhibitors during this time, because otherwise I think that the haematocrit should have increased; but this was not the case. The slowly increasing idEP may be a response to increased blood loss, increased haemolysis or anything else that might provide a slowly growing stimulus to erythropoiesis over the time. In the early seventies Essers experimented with purified erythropoietin preparations but used quantities many times above normal to reach an erythropoietic effect. It is not easy at this moment to get a pure erythropoietin that is generally applicable. At this moment possibly the easiest way is to get rid of toxic inhibitors instead of injecting some sort of erythropoietin.

MUELLER-WIEFEL (Heidelberg) Why did you not look for a correlation with serum ferritin which is a far better indicator of iron status in uraemia than serum iron level?

WALLE We measured the serum iron values because in some papers in the past there has been a correlation between serum iron and erythropoietin levels, and to exclude this point of interrelationship I measured the serum iron values also, not for any other reason.

VAN DER HEM (Groningen) You showed in the slide that the erythropoietin levels were going up all the time during the years. Did you notice also a fall and a subsequent rise on certain occasions?

WALLE Yes, there was one point where the average level of erythropoietin was a little bit lower but all the other ones are in one line as you see (r = 0.76). But I do not know whether there was oscillation or fluctuation with a certain frequency.

VAN DER HEM Was this also influenced by androgen therapy?
WALLE  No, nothing like that.

DRÜEKE  Did you try to correlate your serum immunodetectable erythropoietin levels with serum erythropoietin levels determined using a bio-assay method?

WALLE  Yes, we did, because we rather believe that conflicting results depend upon the measurement of immunodetectable hormones or bio-assay hormones. We tried to get a correlation between the bio-assayed EP levels by means of the polycythaeic mouse and the idEP levels. After transfusions in three patients there was a fall in bio-assayed erythropoietin but not in the idEP levels at all. One patient after a transfusion of 1000ml concentrated erythrocytes had no deviation from his pre-transfusion idEP levels. I do not know the reason for that.