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Serum Erythropoietin Levels in Patients With Solid Tumours

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Patients with malignant disease frequently develop anaemia. To investigate the role of erythropoietin (EPO) in this anaemia, serum levels were determined in patients with solid tumours. The study population consisted of 84 patients (44 males, 40 females) with solid tumours and 99 healthy control subjects, and 13/84 patients were anaemic. Serum EPO was clearly elevated in the anaemic tumour patients, but this increase was less than in patients suffering from iron deficiency anaemia. As in iron deficiency anaemia, the correlation between EPO levels and haemoglobin values was inverse. When compared to healthy control subjects, the levels of EPO in the tumour patients without anaemia were decreased. We conclude that there may be an inhibition in the expression or secretion of EPO in patients with solid tumours which, as yet, has not been further defined. Based on this, the treatment of anaemia in cancer patients with erythropoietin appears promising.

Key words: erythropoietin, anaemia of cancer, solid tumours
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INTRODUCTION

ERYTHROPOIETIN (EPO; molecular weight 34000 Dalton) is produced in the kidneys, and is the major hormone responsible for the regulation of erythropoiesis. The failure to produce sufficient amounts of EPO is the major cause of anaemia in end stage renal disease. This anaemia can be corrected by administration of recombinant human EPO to patients on chronic haemodialysis [1]

Serum levels of EPO are elevated in anaemia, unless there is a coexisting renal dysfunction [2]. The high EPO values of patients with anaemia caused by iron deficiency are generally considered as a reference [3]. For patients with rheumatoid arthritis and coexisting anaemia, a reduced increase in serum EPO has been described [4,5], but this finding has not been confirmed by other authors [6].

Cancer patients frequently develop anaemia without having renal disease. This may be caused by chronic bleeding from gastrointestinal tumours or by displacement of normal bone marrow by tumour cells. Increased retention of transferrin in tumour tissue [7, 8], as well as iron storage in the cells of the reticulo-endothelial system (RES), can further promote this anaemia in cancer patients.

Data on the reaction of serum EPO levels in anaemia of cancer patients is mainly derived from studies of patients with haematological malignancies, such as multiple myeloma. Only a few reports have studied patients with other tumours. To gain more insight into this problem, we studied serum levels of EPO in patients with solid tumours and especially gastrointestinal tumours.

PATIENTS AND METHODS

Patients

Blood samples were drawn from 84 patients (44 males, 40 females) with solid tumours on the day of hospital admission to determine EPO levels, blood counts, creatinine and blood urea, vitamin B12 and parameters of iron metabolism. Patients with haemoglobin level of $\leq$ 11 g/dl were considered anaemic. None of the patients studied had received prior nephrotoxic chemotherapy. All 84 patients had normal values for creatinine and urea. One patient who had received blood transfusion before admission was excluded from the study. The laboratory parameters were determined in the routine programme on the day of sample drawing.

The age, sex distribution and the diagnosis of the analysed patients are shown in Table 1. Gastrointestinal tumours, and especially colorectal cancers, were the prevalent diagnosis.

Controls

Serum EPO levels in 99 healthy individuals (36 males, 63 females) served as controls. Their ages ranged from 18 to 56 years (mean 31.25).

Radioimmunoassay for EPO

Serum samples were stored at −20C° until determination of EPO levels. A radioimmunoassay utilising polyclonal antibody (rabbit) against recombinant human EPO was used [9]. The tracer was ^{125}J-labelled rHu-EPO (Amersham, U.K.). Immunocomplexing was achieved with a second antibody (goat) against rabbit gammaglobulin. Hu-EPO "tissue grade" (Amersham, 75000 U/mg) was used as standard.

Statistical analysis was performed with the aid of the SAS program, version 6.04 (SAS Institute Inc., Cary, North Carolina, U.S.A.).

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Table 1. Age and sex distribution, diagnosis of all investigated tumour patients

	Total (n=84)	Anaemic patients (n=13)	Non-anaemic patients (n=71)
Age (years)			
Mean	55.9	55.5	56.0
Range	20–87	35–69	20–87
Sex			
Male	44	3	41
Female	40	10	30
Diagnosis			
Colorectal cancer	29	5	24
Oesophageal cancer	8	1	7
Gastric cancer	11	2	9
Melanoma	9	0	9
Others	27	5	22

RESULTS

Of the 84 patients, 13 (3 males, 10 females) were anaemic (haemoglobin ≤ 11 g/dl). Females (10/40) were found to be more frequently anaemic than males (3/44).

Serum EPO levels were elevated in anaemic tumour patients (Tabel 2). Below a haemoglobin of 11 g/dl, the EPO concentration increased impressively (Figure 1). The serum iron levels in the anaemic patients were low in comparison to the non-anaemic patients (P 0.0079, Table 2). In addition to EPO and iron levels, the haemoglobin was closely correlated to sex (P 0.004), reticulocytes (P 0.0003) and to transferrin levels (P 0.05, Table 3). Diagnosis, patient age, folic acid, vitamin B12 and ferritin showed no correlation to either EPO levels or haemoglobin concentration. The EPO concentration was not dependent on sex.

The frequency of anaemia was not higher for patients with gastrointestinal tumours than for patients with other tumours (Table 4), even though there were slight differences in the mean haemoglobin values and EPO levels.

Surprisingly, lower erythropoietin values were found in cancer patients who were not anaemic compared to normal controls (P=0.0001, Table 5, Figure 2). In contrast, EPO levels in the anaemic patients were clearly elevated.

DISCUSSION

In physiological response to anaemia, the secretion of the renal hormone EPO is increased. The pronounced elevation of EPO in patients with iron deficiency anaemia is generally considered as reference [5, 6, 10].

Table 2. Haemoglobin, EPO, iron and transferrin levels in tumour patients

	Normal range	Anaemic patients (n=13)	Non-anaemic patients (n=71)	Chi squared test P
Haemoglobin (g/dl)	11.8–18.0	9.7 (1.1)	13.7 (1.5)	<0.0001
EPO (mU/ml)	4–33	35.8 (19.7)	15.0 (5.6)	0.0025
Iron (μmol/l)	7–24	8.8 (12.3)	17.6 (9.6)	0.0079
Transferrin (mg/dl)	170–460	208.3 (97.2)	261.4 (88.9)	0.055

Values expressed as mean (standard deviation).

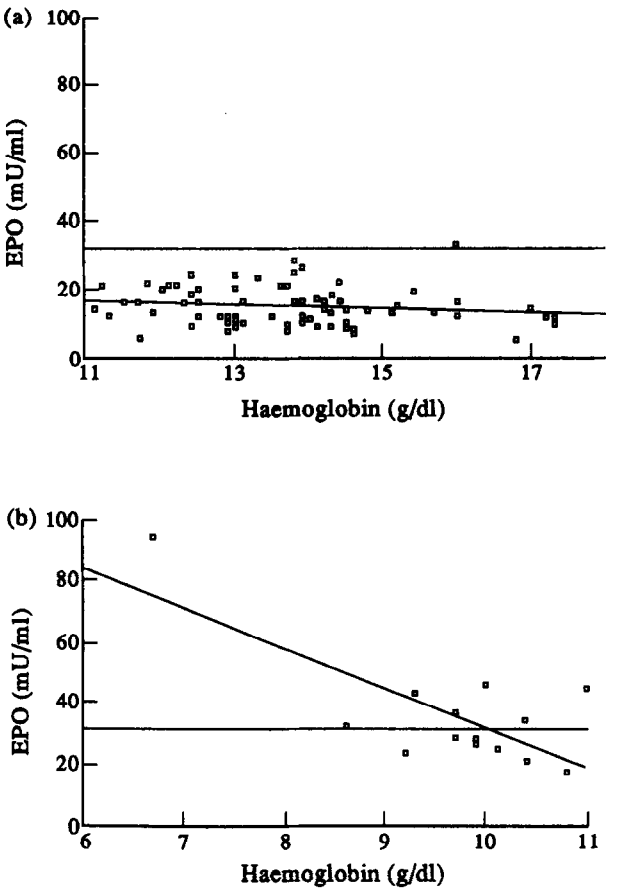

Figure 1. Haemoglobin versus serum EPO in non-anaemic (a) and anaemic (b) patients with solid tumours. Horizontal lines at ~ 30 EPO mU/ml are normal values + 3 S.D.

In this study, we investigated the serum EPO levels in 84 patients with solid tumours. The EPO levels in the anaemic patients (n=13) were elevated (P0.0025), but the concentrations were definitely lower as compared to literature reports for patients with iron deficiency anaemia. These findings are in accordance to those of Miller and colleagues [11] who also found a decreased EPO response to anaemia in patients with solid tumours. In contrast to these authors, we were able to demonstrate that the inverse correlation between haemoglobin and EPO levels is unchanged in comparison to patients with iron deficiency anaemia. Several others have previously reported reduced EPO levels in anaemic tumour patients [12–14], but these data were mainly collected from patients with neoplasia of the haematopoietic system. Baer and colleagues [4] could not

Table 3. Correlations between different serum values

	Haemoglobin	EPO levels	Iron concentration
Age (years)	n.s.	n.s.	n.s.
Sex	P 0.004	n.s.	n.s.
Diagnosis	n.s.	n.s.	n.s.
Reticulocytes	P 0.0003	P 0.002	P 0.06
Folinic acid	n.s.	n.s.	n.s.
Vitamin B12	n.s.	n.s.	n.s.
Transferrin	P 0.05	P 0.01	n.s.
Ferritin	n.s.	n.s.	n.s.

n.s., non-significant.

Table 4. Haemoglobin and EPO for different diagnosis groups

	Total	Anaemic patients	Non-anaemic patients
Gastrointestinal tumours			
n	48	8	40
Age (years)	60.2	58.4	61.0
Sex			
Male	29	2	28
Female	19	6	12
Haemoglobin (g/dl)	12.9	9.5	13.5
EPO (mU/ml)	19.5	41.0	15.3
Correlation of Hb and EPO			
P value:	0.0001	0.057	n.s.
Coefficient of correlation	−0.65	−0.69	−0.09
Other tumours			
n	36	5	31
Age (years)	50.4	54.0	49.5
Sex			
Male	14	1	13
Female	22	4	18
Haemoglobin (g/dl)	13.5	10.0	14.0
EPO (mU/l)	16.5	27.6	14.7
Correlation Hb and EPO			
P value	0.0014	0.012	n.s.
Coefficient of correlation	−0.51	−0.95	−0.17

n.s., non-significant.

Table 5. EPO levels in anaemic tumour patients and healthy controls

	Controls (*n*=99)	Anaemic tumour patients (*n*=13)	Non-anaemic tumour patients (*n*=71)
EPO (mU/ml)			
Mean	21.6	35.8	15.0
S.D.	3.9	19.7	5.6
Range	16–33	17–94	5–33

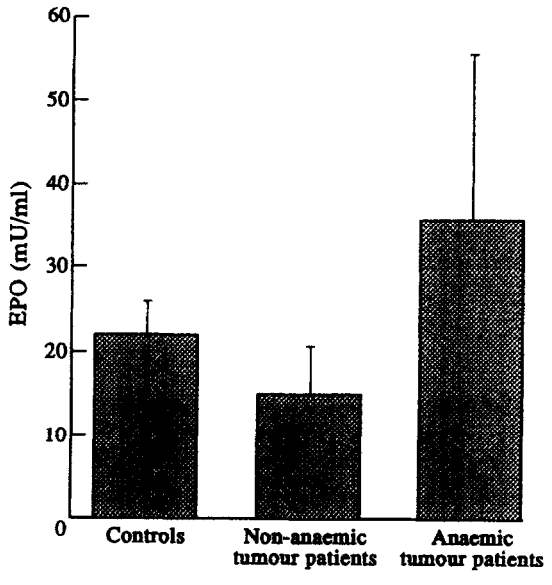

Figure 2. EPO levels in tumour patients and healthy controls (mean ± S.D.)

demonstrate reduced EPO levels in their patients. Data from older reports are based on various bioassays for EPO [15,16], with a sensitivity inferior to that of the radioimmunoassay-(RIA) or enzyme-linked immunoassay (ELISA) which are available today [9, 10, 17].

In our non-anaemic tumour patients, we found lower serum levels of EPO as compared to healthy control subjects ($P<0.0001$). Blood urea nitrogen and creatinine of all our patients were within the normal range, so that renal insufficiency can be excluded as a cause for this finding. If and how the synthesis or the secretion of EPO is inhibited by the malignant disease is not known. It could also be speculated that the turnover of EPO is increased in malignant disease with a negative effect on erythropoiesis.

For patients with malignant diseases of the haematopoietic system, anaemia can be corrected by recombinant human EPO [18]. Our finding that patients with solid tumours have a decreased EPO response to anaemia makes it worthwhile investigating the same treatment for these patients.

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