Effect of Erythropoietin in Normal Men and in Patients with Renal Insufficiency

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Methods

As pure erythropoietin is not available, we obtained erythropoietin-rich plasma by plasmapheresis from patients suffering from aplastic anaemia. The plasma was stored at $-20^\circ\text{C}$ until pooled and assayed for erythropoietic activity using the $^{59}$iron incorporation rate in the polycythaemic mouse system (Essers et al, 1973).

All recipients were O Rh +. The effect of erythropoietin on erythropoiesis was measured by counting the number of reticulocytes.

Results

Infusion of 500 u of erythropoietin in three normal volunteers resulted in a significant increase in the number of reticulocytes per cubic millimetre of blood with maximum response 36 hr later (Figure 1).

Two patients with chronic uraemia and chronic glomerulonephritis on intermittent haemodialysis showed no increase of reticulocytes after receiving 500 u of erythropoietin (Figure 2).

The infusion of 500 u erythropoietin in these two patients was given at the beginning of an eight-hour haemodialysis. We repeated this study giving the erythropoietin at the end of the haemodialysis and again there was no increase in reticulocytes.

One of these patients received twice 935 u of erythropoietin intravenously some months later. He responded with a marked rise in the reticulocyte count (Figure 3).

A patient with uraemia and pyelonephritis on haemodialysis treatment showed a significant increase in reticulocytes after infusion of 2,000 u of erythropoietin (Figure 4).

Two patients suffering from chronic glomerulonephritis who were on
Figure 1. Absolute number of reticulocytes per cubic millimetre of blood of three normal volunteers after a single IV infusion of 500 u of erythropoietin.

Figure 2. Absolute number of reticulocytes per cubic millimetre of blood of two patients with chronic glomerulonephritis on intermittent haemodialysis treatment after a single infusion of 500 u of erythropoietin.

Figure 3. Absolute number of reticulocytes per cubic millimetre of blood of a patient with chronic glomerulonephritis on intermittent haemodialysis after two intravenous infusions of 935 u of erythropoietin.

Figure 4. Absolute number of reticulocytes per cubic millimetre of blood in a patient with chronic pyelonephritis on intermittent haemodialysis after a single intravenous infusion of 2,000 u of erythropoietin.
Figure 5. Absolute number of reticulocytes in two patients with chronic glomerulonephritis on conservative treatment after a single intravenous infusion of 500 u of erythropoietin.

Figure 6. Absolute number of reticulocytes per cubic millimetre of blood of two patients with chronic glomerulonephritis on conservative treatment after a single intravenous infusion of 500 u of erythropoietin.

Figure 7. Absolute number of reticulocytes per cubic millimetre of blood of a patient with chronic pyelonephritis on conservative treatment after a single intravenous infusion of 2,600 u of erythropoietin.

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conservative treatment showed no reticulocyte crisis after infusion of 500 u of 
erthropoietin (Figure 5). Their haematocrits were 33% and 27% and their serum 
creatinine levels 7.6 mg and 16.8 mg per 100 ml, respectively.

On the other hand two patients with chronic glomerulonephritis (haematocrit 
30%, and 31%, serum creatinine 4.2 and 3.5 mg per 100 ml) showed a marked 
increase of reticulocytes after infusion of 500 u of erythropoietin (Figure 6).

A patient with chronic pyelonephritis with severe uraemia, (haematocrit 25%. 
serum creatinine 12 mg per 100 ml) was given 2,600 u of erythropoietin, and he 
reacted with a marked increase in reticulocytes (Figure 7).

These results support the hypothesis that there is a relative resistance to 
erthropoietin in chronic uraemic patients. The resistance to erythropoietin 
seems to be greater in patients with severe uraemia than in patients with only 
slight renal insufficiency.

References

Essers, U, Muller, W and Brunner, E (1973) Klinische Wochenschrift, 51, 1,005

Open Discussion

S SHALDON (Montpellier) Do you have any idea of the molecular weight of 
your inhibiting substances?

ESSERS We can only say that there are substances of high molecular weight 
which inhibit but we do not know what they are.

L GOTLOIB (Israel) Do you have any information about the iron stores of 
your patients before haemodialysis? Did some of your patients who did not 
respond to erythropoietin have iron deficiency, or were they patients with a high 
haemolysis rate? Did you find that androgenic steroids stimulated erythropoietin 
production?

ESSERS We only studied patients who had iron in their bone marrow as measured 
by Prussian blue staining. It is known that steroids alone stimulate renal and 
extra-renal erythropoietin. In some patients we found measurable erythropoietin 
after stimulating with testosterone. It seems possible that testosterone has an 
effect on the stem cells, at least as shown by bone marrow culture

BOSEES Some respond to erythropoietin and some do not. Did those who did 
not respond to testosterone have no response to erythropoietin?

ESSERS We didn’t study the effect of testosterone in these patients who we had 
treated with erythropoietin, but from these results, I am sure that the patients’ 
response to it is a question of the dose of erythropoietin and of the severity of 
the uraemia.

LEBER You have demonstrated that after erythropoietin infusion reticulocytes 
increased in uraemic patients. Was this accompanied or followed by an increased 
haemoglobin haematocrit value, and erythrocyte count as well. Or was it only
an increase in the reticulocyte count?
ESSERS There was only an increase in the absolute reticulocyte count. I think this was due to the fact that we did not have enough erythropoietin to give the patient to stimulate an increase in haemoglobin.