NEFROLOGIA. Vol. X. Suplemento 2. 1990

Clinical use of recombinant human erythropoietin in haemodialysis and CAPD patients

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For many years one of the major obstacles to successful rehabilitation of chronic dialysis patients has been anaemia. The major contributory factor in the development of this anaemia is a relative deficiency of the renal hormone erythropoietin [1, 2]. Until the recent introduction of recombinant human erythropoietin (r-HuEPO) for clinical use, treatment of anaemia in dialysis patients was relatively ineffective and up to 25 % of haemodialysis patients required regular blood transfusion [3]. The other measures used to combat anaemia had included optimization of dialysis, the prevention of iron deficiency and the administration of anabolic steroids.

In 1984 Dr. Joe Eschbach and his co-workers reported the reversal of anaemia in uraemic sheep maintained on haemodialysis by administration of erythropoietin-rich plasma [4] so that when the recombinant hormone (r-HuEPO) was first produced in 1984/5 [5, 6], clinical trials in patients with chronic renal failure were immediately considered. Patients maintained by haemodialysis were used for the initial studies because of the ease of monitoring and administering intravenous r-HuEPO to patients already attending a hospital three times a week. Two groups began clinical trials at about the same time. The group in Seattle compared the effects of different doses of r-HuEPO [7], while the UK group, in Oxford and London, used an escalating dose protocol [8]. The USA study demonstrated a rise in haematocrit, albeit rather slow, at doses as low as 15 IU/kg thrice weekly and a maximum response with doses of 500 IU/kg three times a week. The UK group increased the dose at fortnightly intervals until a response in haemoglobin concentration was seen. Both studies showed that intravenous r-HuEPO therapy could fully reverse the anaemia of chronic renal failure.

The effect of r-HuEPO on the erythroid marrow has been demonstrated by erythrokinetic studies. The activity of the erythroid marrow, estimated by the erythron transferrin uptake, increases with r-HuEPO therapy [7] and is related to the amount of erythropoietin available, endogenous plus r-HuEPO [2]. Bone marrow studies have demonstrated an increase in red cell progenitor, burst-forming-unit-erythroid and colony-forming-unit-erythroid, numbers during the first few weeks of therapy, but a fall in numbers once the haemoglobin is in the maintenance phase [9].

Since 1987 the results of several other trials have confirmed the effectiveness of intravenous r-HuEPO in relieving the anaemia patients on haemodialysis [10-18]. The effect of r-HuEPO is dose dependant, with most patients responding to a dose of 50 IU/kg thrice weekly. As different protocols have required that the haemoglobin or haematocrit be maintained within slightly differing ranges, comparison of maintenance doses is difficult. It appears, however, that a weekly dose of 60-750 IU/kg is usually required, with most patients requiring less than 300 IU/kg per week [18-22]. From the results of one uncontrolled study of 73 patients Bommer et al. [18] have suggested that during the maintenance phase higher weekly doses are required if the r-HuEPO is administered twice rather than three times per week. This impression was corroborated by another multicentre study, of 150 patients, in which the patients receiving twice weekly r-HuEPO to maintain the haemoglobin were also shown to require a higher total weekly dose than the patients receiving thrice weekly injections [22]. Further properly controlled trials are needed to confirm this impression.

Intravenous administration of r-HuEPO results in very high plasma levels immediately after injection which then fall with a $T_{1/2}$ of 4.9 [2] to 9.3 hours [23]. In contrast the maximum levels reached after sub-

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cutaneous administration are lower, but at higher doses (100 IU/kg) levels are sustained above baseline for up to 72 hours [24]. This may lead to more continuous stimulation of the erythroid marrow. Although intravenous r-HuEPO is easily administered to haemodialysis patients both on hospital and home dialysis there is interest in any possible reduction in total dose with subcutaneous administration. One group, studying seven patients, changed the route of r-HuEPO administration from intravenous to subcutaneous once the target haemoglobin had been reached [25]. The dose was reduced by 50 % with no fall in haemoglobin during seven weeks follow up. Another group [26] have reported a reduction of dose by as much as 70 % in patients transferred from intravenous to daily subcutaneous administration. These studies were uncontrolled and included only very small number of patients so it is not yet certain that subcutaneous administration provides a saving in the maintenance r-HuEPO dose.

In many countries a significant proportion of patients requiring dialysis are now maintained by continuous ambulatory peritoneal dialysis (CAPD), and in these patients intravenous administration of r-HuEPO would be impractical. Therefore, interest arose in the feasibility of intraperitoneal or subcutaneous administration.

In rabbits absorption of r-HuEPO from the peritoneum was found to be almost complete, 98 %, when the r-HuEPO was administered undiluted by dialysate during a prolonged dwell period, but was significantly less, at 60 %, in the presence of dialysate [27].

Macdougall et al. have reported the results of intravenous, subcutaneous and intraperitoneal single dose pharmacokinetic studies in CAPD patients. The man $T_{1/2}$ of an intravenous dose of 120 IU/kg r-HuEPO was 8.2 hours [28]. After the same dose given subcutaneously a significant rise in serum erythropoieetin levels was observed by 2 hours with the maximum levels achieved at 18 [28]. The maximum serum levels achieved after subcutaneous administration were only about 4 % of those reached after the same intravenous dose. They have also demonstrated that the dose of intraperitoneal r-HuEPO required to produce a pharmacokinetic profile similar to that obtained after subcutaneous administration is five to ten times the subcutaneous dose [28].

Hughes et al. [24] have also reported pharmacokinetic studies performed using a different formulation of r-HuEPO in patients receiving regular subcutaneous therapy for anaemia. For an intravenous dose of 100 IU/kg the mean $T_{1/2}$ was 4.8 hours, a result similar to that obtained in haemodialysis patients in the same unit [2]. After the same subcutaneous dose maximum levels were achieved at a mean of 12 hours and were sustained above baseline for up to 72 hours. In contrast, when the same dose was administered into the peritoneum in a two litre volume of dialysate with a ten hour dwell, maximum levels were achieved at about 12 hours, but were back to baseline by 22 hours.

Both groups have estimated the «bioavailability», calculated as the area under the pharmacokinetic curve (AUC), of r-HuEPO and compared the three routes of administration. Estimates of the AUC of the subcutaneous route range from 21.5 % [28] to 31 % [24] of the intravenous route. The AUC for the intraperitoneal route is only 46 % of the subcutaneous route [24]. Although the pharmacokinetic studies suggest the total r-HuEPO available is considerably more after intravenous dosing, with high peak levels immediately after dosing falling to below baseline levels prior to the next dose, this mode of administration may not provide sustained stimulation of the erythron. With thrice weekly subcutaneous administration it can be shown that plasma r-HuEPO levels are sustained above baseline levels, providing continuous stimulation of the erythroid marrow.

Despite these differences in pharmacokinetic profiles both the subcutaneous and intraperitoneal routes of administration have been shown to be effective in CAPD patients. Stevens et al. [29] and Macdougall et al. [30] have reported the efficacy of subcutaneous r-HuEPO in adult CAPD patients while Sinai-Trieman et al. [31] have shown its effectiveness in teenage patients maintained by continuous cycling peritoneal dialysis (CCPD). The dose freuency has been thrice weekly and there is a suggestion that CAPD patients receiving subcutaneous r-HuEPO require lower doses than haemodialysis patient receiving intravenous r-HuEPO [29]. One group has demonstrated the effectiveness of intraperitoneal erythropoietin in the treatment of five anaemic CAPD patients [32], although only when given in a small volume (1 litre) of dialysate and during a prolonged overnight dwell (10-12 hr). The mean maintenance required by these patients, 72 IU/kg thrice weekly, is similar to the intravenous dose required by haemodialysis patients in the same unit. This group maintain that the intraperitoneal route is at least as effective as the intravenous route. The subcutaneous route is acceptable to patients, although a minority complain of discomfort after the injection, which lasts only one or two minutes. As there is a possibility of lower doses being required with subcutaneous administration, less risk of peritonitis and no need for adjustment of the dialysis regime it seems likely that the subcutaneous route will become route of choice for CAPD patients.

The majority of patients who have received r-HuEPO to date report relief of the symptoms of anaemia. The almost constant feeling of tiredness is relieved, so that most patients are able to increase their activitis, either in their work or their social life. There are also anecdotal reports of increased appetite [11, 12], relief of

Raynauds' phenomenon [12], improvement in angina [20] and of increased libido [12, 20].

After subjective reports of improvement in exercise tolerance [8] this effect was examined by several groups with formal exercise testing [15, 33-37]. Mayer et al. [15] studied eight haemodialysis patients using cycle ergometer exercise testing at an initial Hb of 5.9 g/dl (SD 0.61) and again after reaching the target haemoglobin of 10 g/dl. The workload at the anaerobic threshold was measured to give an estimate of exercise capacity. This increased from 70 ± 16.9 Watts to 106.9 ± 17.3 Watts with r-HuEPO therapy. Böcker et al. [33] also used cycle ergometer exercise testing, but measured workload at a heart rate of 130 beats/min rather than workload at the anaerobic threshold, to assess exercise capacity in fifteen haemodialysis patients during intravenous r-HuEPO therapy. The workload rose from 73 ± 28 Watts to 98 ± 38 Watts with the rise in haemoglobin from 7.3 ± 1.2 to 11.3 ± 1.7 g/dl. The workload at heart rate 130 beats/min achieved by these patients on r-HuEPO remained low when compared with the value of 125 Watts attained by normal persons. Other groups have confirmed these findings using either cycle ergometer [35-37] or treadmill [34] exercise testing.

An improvement in cardiac function has been demonstrated by studies using indirect measurements of cardiac output during the assessment of exercise tolerance, either by a «rebreathing» method [36], dye dilution [38] or echocardiography [39]. Most of these methods have shown a fall in cardiac size [39] and cardiac output, both at rest and on exercise.

The majority of chronic renal failure patients treated with r-HuEPO report a subjective improvement in their quality of life. Objective assessment of changes in quality of life was considered unnecessary during the early studies of r-HuEPO therapy in haemodialysis patients and it is only as the cost of long-term r-HuEPO therapy has become apparent that the question of optimal haemoglobin concentration has arisen and the need for formal documentation of improvement in quality of life has been required to backup applications for funding of the treatment.

A number of investigators using questionnaires have now provided objective evidence of improvement in quality of life [40-42]. One group has also suggested there is an improvement in cognitive function with r-HuEPO therapy [40] although this remains to be confirmed. The most rigorous studies have been undertaken by the Canadian Erythropoietin Study Group, who have used several methods of assessing quality of life in 118 haemodialysis patients in a double-blind placebo controlled trial. There three groups of patients, one received placebo injections while in the others the haemoglobin was brought up to either 9.5-11 g/dl or to 11.5-13 g/dl. In comparison with the placebo treated patients the r-HuEPO treated patients showed a significant improvement in quality of life [43]. It is interesting that although there was a significant positive correlation of the improvement in quality of life with the increase in haemoglobin concentration there was no significant difference in the quality of life scores between the two r-HuEPO treated groups at a haemoglobin of 9.5-11 g/dl and 11.5-13 g/dl [43]. Therefore, the optimal haemoglobin concentration required for symptomatic relief in patients receiving r-HuEPO remains to be established.

In the early studies of r-HuEPO in haemodialysis patients there were anecdotal reports of increased libido or return of potency [12, 20]. One group has reported normalization of prolactin levels in 16 haemodialysis patients after four months intravenous r-HuEPO therapy [44]. This normalization of prolactin was associated with improved sexual performance in 4 out of 7 males and return of menstruation in 5 females. The same group have also observed a fall in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) with a corresponding rise in testosterone levels. The FSH and LH response to luteinizing hormone releasing hormone (LHRH) was also normalised. In contrast, Bommer et al. [45], who studied 10 male chronic haemodialysis patients found that although 50 % reported improved libido or potency on a questionnaire, there were no changes in prolactin or testosterone levels, nor was there any alteration in the response to LHRH and thyrotropin releasing hormone (TRH).

The major adverse effect of raising the haematocrit is aggravation of pre existing hypertension [7, 8, 11-15, 29]. The mechanism by which treatment with r-HuEPO aggravates hypertension is as yet unclear, but is likely to be related to changes in peripheral vascular resistance. Peripheral vascular resistance increases firstly because increasing the haematocrit increases whole blood viscosity to near normal values [14, 17] and secondly by relief of hypoxia-induced peripheral vasodilation. The effect of increasing haematocrit in raising blood pressure has been examined both in haemodialysis patients receiving blood transfusions [46] and in patients receiving r-HuEPO. Nonnast-Daniel et al. [47], using plethysmography of the calf to measure regional blood flow have observed an increase in regional vascular resistance and a decrease in regional blood flow in haemodialysis patients receiving intravenous r-HuEPO. However, despite these changes tissue oxygenation improved. Another factor may be that changes in plasma volume do not correspond to the rise in red cell volumen, with the effect of temporarily increasing the total blood volume during the period of rising haematocrit. To date there is no evidence for involvement of the renin-aldosterone system [48] or for a direct pressor effect of r-HuEPO [49].

There are a number of reports of seizures occurring during r-HuEPO therapy in haemodialysis patients,

usually in association with hypertension. One patient in the Oxford/Hammersmith group[8], with poorly controlled blood pressure prior to treatment, developed hypertensive encephalopathy and seizures after about 9 weeks therapy and following a rapid rise in haemoglobin of 4 g/dl. The r-HuEPO was stopped and the haemoglobin fell to the pretreatment level in three weeks. The blood pressure was then controlled before restarting r-HuEPO, which was then well tolerated without any recurrence of seizures. In Seattle, one patient with a past history of seizures also had a seizure related to exacerbation of hypertension and phlebotomy was required to rduce the haematocrit and control the hypertension[7]. Two other hypertensive events with seizures have been described[50, 51], both patients required paralysis and ventilation to control status epilepticus, but recovered fully. These events both occurred in the first few weeks of r-HuEPO therapy after there had been a significant rise in haemoglobin concentration. The r-HuEPO was started immediately after blood transfusion, so the rise in haemoglobin due to r-HuEPO occurred on top of the elevation already present as a result of the transfusion. These events were associated with labile blood pressure, although not accompanied by the usual fundal changes associated with hypertensive encephalopathy: retinal haemorrhages, exudates and papilloedema. The aetiology of this syndrome is unclear, although there is speculation that changes in cerebral blood flow, as a result of increased whole blood viscosity and relief of hypoxia, as well as hypertension may contribute. In an attempt to prevent these serious adverse events the present advice is to give r-HuEPO in lower doses than those used in the early clinical trials so that the rate of rise in haemoglobin is below 0.5 g/dl per week. Seizures now appear to be much less frequent, but this may be because of increased awareness of the risks and, hence, closer monitoring of blood pressure and earlier adjustment of antihypertensive therapy.

Influenza-like symptoms occurring after intravenous injection have been reported by several investigators[8, 11, 52, 53], but only in a minority of patients. The patients complain of malaise, bone aches and of feeling feverish. The symptoms start about 30 minutes after injection and may last for several hours. The symptoms do not occur after every injection and vary in severity. They may be eased by slower administration of r-HuEPO or, as the Oxford/Hammersmith patients have found, they can be prevented by aspirin or paracetamol[54], taken during dialysis about 30 minutes before r-HuEPO injection. These symptoms become less severe with time on r-HuEPO therapy and preventative measures are not necessarily required indefinitely[21].

It was anticipated that a reduction in dialyser plasma flow associated with the rise in haematocrit during r-HuEPO therapy would impair the efficiency of haemodialysis, particularly high efficiency short hours dialysis, or haemofiltration[55]. As urea clearance is the least affected by changes in haematocrit assessment of adequate dialysis using urea kinetic modelling may require adaptation to correct for plasma flow. Many clinical trials in haemodialysis patients have reported no change in plasma creatinine, urea or phosphate levels[11-13, 19, 56], whereas others have demonstrated small but statistically significant changes in creatinine[22], urea[7], phosphate[22] and potassium[7]. There are also reports of episodes of hyperkalaemia[11] and one hyperkalaemic death[7]. Formal studies of dialyser efficiency in a small number of patients suggest the increased haematocrit is associated with reduction in dialyser clearances[57]. However, as many clinical trials have not reported changes in dialysis regime the implications of these results are uncertain. The experience in Oxford/Hammersmith is that individual patients may require increased hours of dialysis or size of membrane to control inter-dialysis weight gain, pre-dialysis potassium, creatinine or urea.

Reports of vascular access thrombosis have caused concern[8, 11]. At first it was difficult to be certain that the incidence of failure was any higher than in untreated haemodialysis patients, however, one placebo controlled double-blind study[58] has confirmed the increased risk in r-HuEPO treated patients. There is an impression that thrombotic events are more likely to occur in access sites with a past history of problems[52]. Another consequence of the increased haematocrit is clotting in the dialyser and many groups have noted an increase in heparin requirements[12, 19, 20, 52].

The tendency for r-HuEPO treatment to increase the risk of thrombosis suggested that it may have a beneficial effect on the bleeding diathesis associated with uraemia. The test which correlates best with the presence of a bleeding diathesis in uraemic subjects is the skin bleeding time, as measured by the Ivi method or a modern variation of it[59]. The prolonged skin bleeding time often found in uraemic subjects is related to the reduced haematocrit and can be corrected by red cell transfusion[60, 61] and r-HuEPO therapy. Moia et al.[62] studied seven haemodialysis patients with markedly prolongd bleeding times and mild bleeding symptoms who received intravenous r-HuEPO for anaemia. Six patients had correction of their bleeding time and resolution of the mild bleeding symptoms. The bleeding time in the seventh patient showed some improvement although it did not reach the normal range. This improvement in bleeding time was associated with improvement in adhesion of platelets to the subendothelium of human umbilical arteries.

The optimal haemoglobin concentration, giving maximal symptomatic improvement, while keeping the risks of hypertension and vascular problems to a

minimum is, as yet, unclear. However, it is apparent that r-HuEPO has already revolutionised the lives of many patients and will be in great demand in the future.

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