Non-cardiac benefits of human recombinant erythropoietin in end stage renal failure and anaemia

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Abstract

Recombinant human erythropoietin (r-HuEpo) is now available to correct the anaemia of end stage renal failure. The clinical consequences of increasing the haemoglobin concentration in children on dialysis are incompletely documented; a placebo controlled study is essential when assessing subjective changes, for example in appetite or other aspects of quality of life.

A single blind, placebo controlled crossover study in 11 children with end stage renal failure was performed to assess the clinical benefits resulting from correction of anaemia. Ten of the 11 children completed 36 weeks of the study and seven completed both 24 week limbs. Subcutaneous administration of r-HuEpo twice a week resulted in an increase in haemoglobin concentration, from 73 to 112 g/l. This was associated with an objective improvement in exercise tolerance, and a subjective improvement in physical performance and health, and better school attendance. No consistent effect was seen on appetite, growth, psychosocial functioning, biochemical control, or peritoneal dialysis efficiency. A small but clinically unimportant increase in systolic and diastolic blood pressure was seen in five children. One child on antihypertensive treatment required an increase in dosage during r-HuEpo while another child required a reduction in treatment.

These findings, together with the important cardiac benefits previously described during r-HuEpo treatment, support the use of r-HuEpo in all children with end stage renal failure and anaemia.

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A deficiency of erythropoietin is the single most important factor contributing to anaemia in end stage renal failure. Anaemia may be responsible for several of the clinical features of end stage renal failure in children, such as reduced exercise tolerance, fatigue, poor appetite, and impaired growth. With the characterisation and manufacture of recombinant human erythropoietin (r-HuEpo) in recent years it has become possible to correct anaemia and to assess which of these clinical features are attributable to anaemia.

An extensive list of benefits of r-HuEpo have been reported in adult patients.¹ Although a limited number of studies of r-HuEpo in

children with end stage renal failure have confirmed its efficacy in correcting anaemia,²⁻⁴ none of these has been placebo controlled, making it impossible to interpret critically many of the effects ascribed to r-HuEpo. The present study was therefore designed as a single blind, placebo controlled crossover study in order to remove any bias that undoubtedly exists towards a new drug as heavily publicised as r-HuEpo and to assess the effects of r-HuEpo on quality of life, diet, exercise tolerance, and peritoneal dialysis efficiency in a group of children with end stage renal failure on long term peritoneal dialysis. The cardiac benefits of r-HuEpo have been previously reported.⁵

Patients and methods

Eleven children (nine boys, two girls) were enrolled into the study. Their median age was 6.7 years (range 2.3-12.3), and median haemoglobin concentration 73 g/l (range 42-81). The range of underlying conditions and other clinical details are summarised in the table. Ten of the children were on dialysis at the time of the study: peritoneal rapid overnight dialysis in nine cases and haemodialysis in one. Five children were receiving treatment for hypertension but all were normotensive, assessed with regular home blood pressure monitoring (Waeschle DS40).

The design was a single blind, placebo controlled, crossover study with two equal limbs of 24 weeks' duration. The study was approved by the Newcastle health authority ethics committee. Six children were allocated by stratified randomisation to receive r-HuEpo for 24 weeks followed by placebo (group 1; table), and five the reverse treatment order (group 2; table). r-HuEpo (Recormon, Boehringer Mannheim) or placebo were administered subcutaneously twice a week by the child or parent at home. The volume of all injections was fixed at 0.5 ml. r-HuEpo was commenced at 50 U/kg/week and increased in stepwise increments to a maximum of 400 U/kg/week by week 12, and thereafter adjusted to maintain a target haemoglobin concentration of 105-120 g/l. In some cases this was achieved with a once weekly subcutaneous injection of r-HuEpo; this was balanced by a similar regimen during the placebo limb to avoid a treatment difference between limbs. Seven children completed both 24 week limbs of the study, two completed the r-HuEpo limb and half of the placebo limb, one completed the placebo limb and half of the r-HuEpo limb,

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Clinical details of the 11 children entering the study

Patient No	Sex	Age (years)	Haemoglobin (g/l)	Dialysis duration (years)	Mode of dialysis	Diagnosis	Treatment for hypertension	No of weeks in study
Group 1 (r-HuEpo/placebo)								
1	M	10.4	42	3.2	PROD	Familial HUS	Yes	48
2	M	2.8	72	2.5	PROD	Dysplasia	No	48
3	F	4.5	81	3.8	PROD	Dysplasia	No	48
4	M	3.0	80	1.7	PROD	Congenital nephrotic syndrome	Yes	48
5	M	6.4	73	3.1	Haemodialysis	Posterior urethral valves	No	40
6	F	8.9	66	0.4	PROD	Unknown	Yes	36
Group 2 (placebo/r-HuEpo)								
7	M	12.3	76	0.4	PROD	FSGS	Yes	38
8	M	8.8	68	0	None	*Reflux associated dysplasia	No	48
9	M	6.7	76	3.2	PROD	Dysplasia	No	48
10	M	2.3	64	1.0	PROD	Recessive PCKD	Yes	30
11	M	8.8	75	7.9	PROD	Posterior urethral valves	No	48

PROD=peritoneal rapid overnight dialysis; HUS=haemolytic uraemic syndrome; PCKD=polycystic kidney disease; FSGS=focal segmental glomerulosclerosis.

*Patient with Duchenne muscular dystrophy.

and one completed only the placebo limb (table). Three children withdrew because they underwent renal transplantation and one child died of hepatic fibrosis, related to underlying polycystic disease.

EXERCISE TOLERANCE

This was assessed in two ways. Firstly, the 2 minute walking distance was measured.⁶ Each child was asked to walk as fast as possible up and down an enclosed section (25 metres) of hospital corridor with no gradient. Simple encouragement was given and, in view of a possible training effect, the greater of two distances was used in the analysis. Seven of the 11 children were judged old enough to participate.

Secondly, six of the older children also underwent formal treadmill exercise testing (Marquette instruments) using either a Bruce protocol (n=3) or a modified Bruce protocol (n=3).⁷ The duration of exercise and the total workload (calculated by Marquette software) was recorded in addition to the heart rate response to exercise and the electrocardiographic waveform was analysed for evidence of ischaemia or arrhythmia.

QUALITY OF LIFE

This was assessed by means of a 25 part parental questionnaire, applying a modified format of a previously used questionnaire (appendix).⁸ The questions covered various aspects of the child's well being and behaviour including mood and psychological behaviour, social interaction, somatic complaints and general health, sleep, diet, school functioning, and physical performance. Parents completed the questionnaire during the two week run-in period before the study and at the end of each limb. A visual analogue scale (10 cm) was used to score each question, with the best and worst possible responses at each end of the scale. Parents were allowed to see their previous assessments and movements of less than 5 mm away from the previous mark were ignored. Each of the first 23 questions was analysed separately and then those questions covering a common area, such as physical performance

and health (Q6, 7, 15, 18, 22, 23), diet (Q10–12), psychosocial behaviour (Q5, 8, 9, 13, 14, 16, 17, 19), school performance (Q20, 21), and sleep behaviour (Q1–4) were grouped together. Finally, the global score, incorporating all 23 questions, was calculated. In addition a further question (Q24) was included to assess, in as general a way as possible, whether the parents had observed any overall improvement in the child during either treatment period. Finally, at the end of the study each parent was asked to identify the treatment order that their child had received.

DIETARY INTAKE

A prospective three day dietary diary of all food consumed was completed by the parents during the two week run-in period before the study and every 12 weeks during the study. Each parent was asked to record all food and drink taken in terms of type and quantity, including nasogastric feed in the four children on overnight nasogastric tube feeding. This type of assessment is very familiar to these parents, forming part of routine patient management. A senior dietitian (SW), who was unaware of the treatment order, calculated the mean daily energy, protein, potassium, and phosphate intake for each period.

ANTHROPOMETRIC MEASUREMENTS

Every four weeks weight, height, triceps subcutaneous fat thickness (Harpender Skinfold Caliper, British Indicators, Luton) and mid-arm circumference were measured. Weight, height, and mid-arm circumference velocity were calculated for each limb by fitting a regression line through all data points and these velocities were used in the analysis.

PERITONEAL DIALYSIS STUDY

Peritoneal dialysis efficiency was assessed using a 30 minute equilibration study at the end of each limb of the study.⁹ This involves running a known volume of dialysis fluid into an empty peritoneal cavity and taking two timed dialysis fluid samples over a period of 30

minutes, together with a single blood sample. Measurement of potassium, urea, creatinine, glucose, and phosphate on each specimen allows estimation of the half life for equilibration across the peritoneal membrane for each substance. In addition the volume of ultrafiltrate removed after each overnight dialysis was recorded and the mean of 10 consecutive nights calculated at the end of each limb.

LABORATORY MEASUREMENT

Full blood count was measured every two weeks using a Coulter counter ('STKS', Coulter Electronics, Luton). Several measures of iron status were taken and the results have been reported in detail elsewhere.¹⁰ Plasma viscosity, creatinine and electrolytes, calcium, phosphate, bilirubin, aspartate transaminase, alkaline phosphatase, albumin, and parathyroid hormone were also measured regularly. Serial r-HuEpo concentrations were measured at a constant interval after the last dose in each child; this interval ranging from 2.5 to 4 days in different children. Serum r-HuEpo concentration was measured using a radioimmunoassay (Boehringer Mannheim).

BLOOD PRESSURE

Each child had their resting blood pressure recorded twice a week at home using an automatic blood pressure machine (Waesche DS40). The same site of measurement and cuff size was used throughout in each child.

STATISTICAL ANALYSIS

Treatment effects were calculated using statistical methods appropriate for the analysis of crossover trials, after excluding a significant period effect.¹¹ To test for the presence of a treatment effect the difference in any measured variable between week 24 (end of period 1) and week 48 (end of period 2) is calculated, and the mean difference found in group 1 compared with that found in group 2, using a standard two sample *t* test. In the absence of a treatment effect the differences are the same and the *t* test non-significant.

Certain variables were only measured at the end of each 24 week limb (treadmill exercise test, peritoneal dialysis study) and the analysis therefore includes only those children completing both limbs of the study. Other

variables, however, were measured every 12 weeks throughout the study (2 minute walking distance, quality of life questionnaire, dietary intake) and it was therefore possible to include data from the three children who completed 36 weeks of the study but failed to complete both limbs. For these variables the mean of the measurements taken during each limb was used in the analysis. Blood pressure readings from these children were also included in the analysis. We felt that use of their data was justified because after 12 weeks of r-HuEpo their haemoglobin concentrations had already risen significantly (from 72 to 99 g/l) and within 12 weeks of stopping r-HuEpo their haemoglobin concentration had fallen to baseline values (from 103 to 67 g/l). The Wilcoxon signed rank sum test was used to assess the responses to the individual questions on the questionnaire while the group data is presented as the confidence interval for the difference between the treatment limbs, after summing the responses to related individual questions.

To analyse the weight, height, and mid-arm circumference data a within-patient comparison was made of the velocities during both limbs using a paired *t* test. A within-patient comparison is vital in view of the large variability in background growth velocities in different children. Lastly, the possibility of a transient effect of r-HuEpo on certain laboratory variables (white cell count, platelet count, serum r-HuEpo concentration) was assessed by looking separately at sequential data from the nine children who completed a 24 week limb of r-HuEpo.

Results

HAEMATOLOGICAL RESPONSE

The median haemoglobin rose from 73 g/l (range 42–81) at baseline to 112 g/l (range 95–142) after 24 weeks r-HuEpo ($p < 0.001$; fig 1). Five children developed evidence of iron deficiency but responded to iron supplementation; four responded to oral treatment but one child was intolerant of oral iron and required intravenous iron.¹⁰ Once the target haemoglobin had been reached it was possible to maintain it in four of the children on a once weekly dose regimen. At the end of the 24 week r-HuEpo limb the mean weekly maintenance dose was 196 U/kg. No significant change in platelet count, white cell count, or plasma viscosity was found during r-HuEpo.

BIOCHEMISTRY

No significant change occurred in sodium, potassium, urea, creatinine, calcium, phosphate, albumin, bilirubin, aspartate transaminase, alkaline phosphatase, or parathyroid hormone concentration.

EXERCISE TESTING

The 2 minute walking distance increased during the r-HuEpo limb in the seven children in whom data from both limbs is available ($p = 0.06$; fig 2A). Only three children

Figure 1 Individual changes in haemoglobin in all 11 children entered into the study.

Figure 2 Changes in exercise tolerance measured by (A) 2 minute walking distance ($n=7$) and (B) total workload during treadmill exercise testing (expressed as a percentage of baseline) ($n=6$).

completed treadmill exercise testing during both limbs; compared with placebo a marked increase in workload was seen during r-HuEpo ($p=0.07$; fig 2B). A change in the heart rate response to exercise was seen after r-HuEpo with a reduction in heart rate at rest ($p=0.002$) and at each successive stage of the exercise test. No arrhythmias or ischaemic changes were seen during either limb.

QUALITY OF LIFE

Four of the 23 individual questions scored significantly better during r-HuEpo ($p<0.05$; numbers 6, 15, 18, 23). In addition the response to the final question (number 24) suggested an overall improvement in the children during r-HuEpo ($p<0.05$).

After grouping related questions together an improvement was found in those questions relating to physical performance and general health, including a better school attendance ($p<0.02$). No significant change was found in the other areas. Figure 3 shows the change in group scores after r-HuEpo, represented as confidence intervals for the difference between r-HuEpo and placebo. The global score, incorporating all questions, showed an increase though this did not reach significance ($p=0.18$).

Of the seven children who completed both limbs of the study five sets of parents identified the treatment order that their child had received, and all were correct. Two sets of parents were unable to detect a noticeable difference between limbs, despite increases in haemoglobin from 68 to 142 g/l and from 64 to 109 g/l.

DIETARY INTAKE

No significant change in total energy, protein, potassium, or phosphate intake could be

attributed to r-HuEpo, though total energy intake tended to increase ($p=0.19$). Repeat analysis after adjustment for nasogastric feed intake produced a similar result. Individual parents, however, noticed a marked improvement in appetite during r-HuEpo which disappeared during placebo.

ANTHROPOMETRIC MEASUREMENT

No significant increase in weight ($p=0.21$) or height velocity ($p=0.21$) was seen during r-HuEpo though again individual children showed an increased weight velocity during r-HuEpo relative to placebo. An increase in mid-arm circumference velocity was seen during r-HuEpo, though this failed to reach statistical significance ($p=0.09$). There was no comparable increase in triceps skinfold thickness though there was a greater variability in results, largely attributable to poor cooperation in some of the younger children who found the procedure uncomfortable.

PERITONEAL DIALYSIS STUDY

No change in the peritoneal equilibration of potassium, urea, phosphate, glucose or creatinine, or in the ultrafiltrate volume after overnight dialysis, occurred during r-HuEpo.

BLOOD PRESSURE

Complete blood pressure profiles were available in only seven of the children because the other parents did not keep a consistent written record. Mean values were calculated from 10 consecutive readings at the end of each limb or, in three cases, from the last 10 readings before withdrawing from the study. Of the four children already on antihypertensive treatment one required an increase and one a reduction in therapy. Analysis of the remaining five children, three of whom were not on antihypertensive treatment during the study, showed an increase in systolic blood pressure during r-HuEpo ($p<0.05$). However, this was a small increase (maximum 6.4%) and did not require any change in treatment. Mean diastolic blood pressure also increased slightly in the three children in whom it was recorded.

Figure 3 Quality of life questionnaire responses after grouping related questions ($n=10$). Presented as the mean percentage difference after r-HuEpo relative to placebo, with the 95% confidence intervals for the difference.

Figure 4 Sequential serum r-HuEpo concentrations during the placebo ($n=9$) and r-HuEpo ($n=9$) limbs. Median values and interquartile ranges shown.

SERUM r-HuEpo CONCENTRATION

Over the course of the 24 weeks of r-HuEpo treatment there was a progressive increase in serum r-HuEpo concentration, though there was considerable individual variation. By comparison serum r-HuEpo concentration remained fairly constant during the placebo limb (fig 4).

Discussion

Approximately 120 children in the UK are currently in end stage renal failure and on dialysis. The vast majority are anaemic and, until very recently, many were transfusion dependent, exposing them to the risks of viral transmission, iron overload, and antigen sensitisation. It is now clear that r-HuEpo is able to reverse the anaemia in virtually all cases, though various factors, in particular iron deficiency, may reduce its efficacy. r-HuEpo is able to abolish transfusion dependency with obvious advantages, including a reduction in HLA sensitisation¹² and the potential of easier transplantation. What is much less clear, however, is what other benefits can be attributed to r-HuEpo. Too many studies have ignored the need for a placebo controlled design particularly when assessing subjective changes, for example in quality of life, amid the positive publicity that surrounded the introduction of r-HuEpo into clinical practice.

Undertaking a placebo controlled study of r-HuEpo in children is difficult because parents and children need to consent to a prolonged period of placebo injections. In addition each centre has only a small number of eligible patients. Although this was a small study, we feel that the inclusion of a placebo period and the crossover design provided more meaningful data than could have been obtained from a much larger uncontrolled study. Previous studies in children have all been uncontrolled and have predominantly involved older children given intravenous r-HuEpo at the end of haemodialysis. We were able to confirm that subcutaneous administration of r-HuEpo twice a week is able to correct anaemia once an adequate supply of iron is present.¹⁰ No change in platelet count was found during this study, in contrast with previous studies, in both adults¹³ and children,¹⁴ which documented an early increase in platelet count on r-HuEpo. These studies involved

intravenous administration of r-HuEpo, which has a very different pharmacokinetic profile and achieves a much higher peak plasma concentration than subcutaneous r-HuEpo.^{15 16}

Important cardiac benefits of short term r-HuEpo treatment in this cohort of patients have already been reported,⁵ with a reduction in cardiac output and ventricular hypertrophy. In addition correction of anaemia is able to improve aspects of quality of life and to have a beneficial effect on exercise tolerance.

The specific questions within the quality of life questionnaire showing significant improvements after r-HuEpo were those reflecting less fatigue and breathlessness during exercise, improved general health, and better school attendance. In addition the final question, which attempted to summarise any overall change for the better on r-HuEpo, scored significantly better. Grouping related questions together confirmed an improvement in physical performance and health but failed to show any significant change in psychosocial, diet, school, or sleep behaviour. These findings are very similar to a large double blind study in adult dialysis patients looking at quality of life, which found an improvement in fatigue, strength, and physical symptoms without a consistent effect on psychological functioning or sleep disturbance.¹⁷ Although the majority of parents were able to correctly identify their child's r-HuEpo/placebo treatment order, two sets of parents were unable to do so despite a dramatic rise in haemoglobin, reflecting how well some children are able to compensate for severe anaemia. One of these children, however, had muscular dystrophy and clearly was not able to benefit from the improved physical performance seen in the other children.

Previous studies in children have documented improved exercise tolerance and an increase in peak oxygen consumption and ventilatory anaerobic threshold after r-HuEpo.^{3 12 18} The importance of including a control group was, however, shown in one of these studies in which the control group also showed a significant improvement in exercise tolerance over the 16 week observation period.¹⁸ In our study both measures of exercise tolerance showed clear improvement after r-HuEpo, although the small number of children prevented this reaching statistical significance.

Previous uncontrolled studies in children have suggested an improvement in appetite associated with r-HuEpo,¹⁹ but we were unable to confirm this with either the record of dietary intake, the parental assessment of appetite on the questionnaire, or with changes in weight velocity. Individual parents, however, commented on marked improvements in appetite during r-HuEpo. In addition an increase in mid-arm circumference velocity was seen. It is possible therefore that a large study might be able to document an improvement in appetite and weight velocity. r-HuEpo did not result in any improvement in height velocity, confirming previous observations,²⁰ and making it unlikely that anaemia contributes to the growth failure of end stage renal failure.

An increase in packed cell volume, coupled with a reduction in cardiac output, could theoretically reduce peritoneal dialysis efficiency by reducing effective plasma flow to the peritoneum. In practice our study, and the majority of studies in adults,^{21 22} found no change in either dialysis efficiency or in ultrafiltrate volume, though others have reported an increase in ultrafiltrate,²³ with either an increase²³ or decrease²⁴ in solute transport. In keeping with an unchanged dietary intake and peritoneal dialysis efficiency we found no change in plasma potassium, urea, creatinine, or phosphate concentrations during r-HuEpo treatment.

The development, or exacerbation, of hypertension is the commonest reported side effect of r-HuEpo administration, on occasions leading to encephalopathy.²⁵ Patients with pre-existing hypertension at the start of treatment may be particularly at risk. During this study only one child with pre-existing hypertension required a marked increase in antihypertensive treatment during r-HuEpo. By contrast a minority of patients actually show a fall in blood pressure on r-HuEpo^{3 26}; one child required a marked reduction in antihypertensive treatment during the r-HuEpo limb, probably as a result of a fall in cardiac output, followed by an increase in treatment during the placebo limb once his haemoglobin had fallen again. In the remaining children a small increase in both systolic and diastolic blood pressure was seen, though this did not necessitate any change in antihypertensive treatment. This increase in blood pressure was not evident in a previous analysis of this patient group,⁵ in which a single blood pressure reading only was taken at the time of echocardiography, stressing the importance of repeated measurement to minimise the inherent variability of blood pressure.

Although the bioavailability of r-HuEpo after subcutaneous injection is only 21–40% that of intravenous r-HuEpo,^{15 16} its longer half life allows a more sustained action and produces a greater erythropoietic response for an equivalent dose.²⁷ The absorption and elimination of subcutaneous r-HuEpo does not appear to change with long term treatment.²⁸ The progressive increase in serum r-HuEpo concentration seen over the course of the r-HuEpo limb is compatible with published pharmacokinetic data in children.¹⁵ With a half life of 21 hours the serum concentration will remain significantly above the predose concentration for at least four days after a subcutaneous dose of r-HuEpo. If the bone marrow sensitivity to r-HuEpo remains unchanged, a progressive reduction in dose requirement would be predicted if administered twice weekly by subcutaneous injection.

In conclusion, correction of anaemia with r-HuEpo is associated with an objective improvement in exercise tolerance and a subjective improvement in physical fitness and health, including better school attendance. These benefits, together with the important cardiac benefits already reported, support the use of r-HuEpo in all children with end stage renal failure and anaemia.

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Appendix

Parental questionnaire together with the descriptions used at opposite ends of each linear analogue scale.

1. How long does he/she sleep each night (to nearest hour)?
2. How long does he/she sleep during the day (to nearest hour)?
3. How easy is it to get him/her settled at night?
Very easy/very hard
4. How often does he/she wake up at night?
Very often/never
5. How often does he/she cry?
Very often/never
6. How is his/her general health at present?
Very good/very bad
7. How active is he/she?
Very active/not at all active
8. Does he/she appear anxious or worry a lot?
Very often/never
9. How often does he/she have tantrums?
Very often/never
10. How is his/her appetite?
Very good/very poor
11. How fussy is he/she about his/her food?
Very fussy/not at all fussy
12. How often does he/she vomit?
Very often/never
13. How well does he/she get along with other children?
Very well/not at all
14. Is he/she pleasant or bad tempered?
Very pleasant/very bad
15. During exercise does he/she get tired easily?
Very easily/not at all easily
16. Is he/she generally happy at present?
Very happy/very unhappy
17. How well does he/she do what he/she is told?
Very well/not at all well
18. How breathless is he/she after exercise?
Very breathless/not at all
19. How well does he/she concentrate on the job at hand?
Very well/very poorly
20. Does he/she enjoy school?
Very much/not at all
21. How is his/her school work at present?
Very good/very poor
22. What is he/she like after school?
Full of beans/very tired
23. How many days has he/she missed school through poor health in the last 3 months?
24. Have you noticed any overall change in him/her over the past 3 months?
Much better/much worse
25. Which do you think he/she has been receiving?
r-HuEpo/placebo/not sure

(Questions 20–23 for schoolchildren only)