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Brief report

Low-dose erythropoietin is effective and safe in children on continuous ambulatory peritoneal dialysis

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Abstract. Hypertension is one of the most important complications of erythropoietin (rHuEPO) therapy in dialysis patients. In this study, the effect of two different dosage regiments of subcutaneous rHuEPO on blood pressure [BP] was evaluated in 20 anemic children on continuous ambulatory peritoneal dialysis (CAPD). Patients were randomized to receive rHuEPO 50 U/kg, either once a week (group 1, 50 U/kg per week) or three times a week (group 2, 150 U/kg per week). At the beginning of the study, 8 patients in group 1 and 8 patients in group 2 were on antihypertensive therapy. In group 1, the hematocrit increased gradually and significantly from 18.98% ± 1.79% to 30.1% ± 1.62% after 6 months, while in group 2 it rapidly increased from 19.53% ± 1.86% to 32.4% ± 1.11% after 3 months. A significant increase in the mean arterial BP was observed in group 2. Antihypertensive therapy had to be increased in all of the 8 previously hypertensive patients and had to be initiated in 1 of the 2 originally normotensive patients in the same group. None of the patients in group 1 required a change in antihypertensive medication. We conclude that during treatment with rHuEPO preexisting hypertension and the dose of rHuEPO are the most important risk factors for the development or worsening of hypertension in children on CAPD, and gradual elevation of hematocrit by low-dose rHuEPO avoids the development of severe hypertension.

Key words: Continuous ambulatory peritoneal dialysis – Recombinant human erythropoietin therapy – Hypertension

Introduction

Correction of anemia by intravenous or subcutaneous (SC) recombinant human erythropoietin (rHuEPO) therapy has been demonstrated in children on continuous ambulatory peritoneal dialysis (CAPD). SC injections are the preferable route of administration [1]. However, there is no information available about the safe dosage and the frequency of administration required to increase hemoglobin to a desirable level without adverse effects [1–4]. The dose regimen recommended for hemodialysis patients can not be applied to CAPD, as the response is exaggerated and the treatment is associated with side effects that may limit its application [3], with the development or aggravation of hypertension being the most important [1, 3, 5]. To assess the effect of rHuEPO treatment on blood pressure (BP) in children, we investigated two dose regimens of SC rHuEPO treatment in 20 CAPD patients.

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Patients and methods

Patients. Twenty anemic patients (13 males, 7 females) aged 5–16 years, (mean 10.55 ± 2.93 years) who had been clinically stable on CAPD for at least 3 months were enrolled in the study. Primary renal diseases were reflux nephropathy (10 patients), urolithiasis (5 patients), chronic glomerulonephritis (3 patients), hemolytic uremic syndrome (1 patient), and amyloidosis (1 patient). Informed consent was obtained from the patients and/or their parents. No causes other than uremia accounted for the anemia. All patients had a hematocrit (Hct) less than 24%, transferrin saturation more than 20%, and a serum ferritin level at least 100 μg/l before therapy. Ferrous sulphate (6–8 mg/kg orally three times a day) was administered to each patient. Patients who had labile or uncontrolled hypertension were excluded. Sixteen patients entered the study on continuous long-standing antihypertensive therapy because of manifest hypertension. The drugs preferentially used for treatment included calcium channel blockers, angiotensin converting enzyme inhibitors, β-blockers, and vasodilators. Four patients had borderline BP without medication. CAPD remained unchanged during the study, exchanging 30–50 ml/kg of 1.36% and/or 2.27% dextrose solution four times daily.

Study design. The study group was observed for 3 months before initiating rHuEPO therapy and then for 6 months after therapy was begun. In the period prior to the study, 85% of patients required blood transfusions for symptomatic anemia. Patients were randomized to receive rHuEPO 50 U/kg, either once a week (Group 1, 50 U/kg per week) or three times a week (group 2, 150 U/kg per week) SC into the

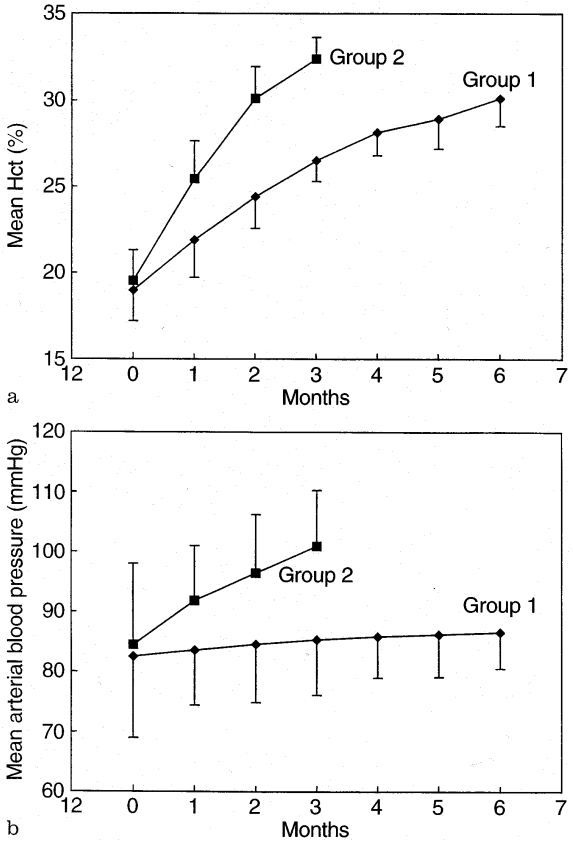

Fig. 1. a Hematocrit (*Hct*) and **b** mean arterial blood pressure in groups 1 and 2 during recombinant human erythropoietin therapy expressed as mean + SD (■—) and - SD (◆—)

upper arm. There were 10 patients in each group. Patients of the two randomized groups did not differ in age, sex, or underlying disease. The characteristics of the two groups at baseline were similar, with a mean Hct of 18.98% ± 1.79% and 19.53% ± 1.86% and a mean arterial BP of 82.46 ± 14.53 and 84.45 ± 13.86 mmHg in groups 1 and 2, respectively. During the initial 12 weeks of therapy, the patients were examined at the hospital twice or three times a week and then once every 2 weeks by one of the research physicians. BP was measured before and at 15-min intervals for 2 h after each rHuEPO injection. Hypertension was defined as BP greater than the 95th percentile for age as indicated by the Task Force on Blood Pressure Control in Children [6]. Mean arterial BP was calculated as systolic pressure plus 2 × diastolic pressure divided by 3 [7]. Complete blood count was measured weekly by coulter counter. The target Hct was defined as an increase in Hct to 30%–32%. Serum iron and total iron binding capacity were determined every month. A complete serum chemistry profile and ferritin levels were assessed monthly. Statistical analysis was performed using Student's *t*-test. Differences were considered significant if the P value was less than 0.05. Data were expressed as mean ± SD.

Results

All 20 patients responded to the rHuEPO treatment with an increase in the Hct level and none required blood transfusions during the study period. The mean Hct in group 1 increased gradually but significantly from 18.90% to 30.10% ($P < 0.001$) after 6 months of 50 U/kg weekly therapy, whereas in group 2 it increased rapidly from 19.50% to 32.40% ($P < 0.001$) and all patients reached the target Hct after 3 months (Fig. 1). None of our patients had a Hct rise of more than 4% per 2 weeks during the study period.

Mean arterial BP in group 1 increased gradually but not significantly from 83 mmHg to 87 mmHg after 6 months of therapy, but in group 2, in which the weekly dose of rHuEPO was tripled, a statistically significant ($P < 0.05$) rise in the mean arterial BP (from 85 mmHg to 101 mmHg) was observed at the end of the 3rd month (Fig. 1). This increase occurred despite an increase in the dose and number of antihypertensive agents used. At the beginning of the study, 8 patients in group 1 and 8 patients in group 2 were on antihypertensive therapy because of manifest hypertension. Antihypertensive therapy had to be increased in all of the 8 patients who were already on antihypertensive medication prior to the study and had to be initiated in 1 of the 2 originally normotensive patients in group 2. Due to problems with the management of hypertension, rHuEPO therapy had to be discontinued for a short period in 4 patients (2 of whom had hypertensive encephalopathy) in the same group. None of the patients in group 1 required a change in antihypertensive medication.

After attainment of the target Hct after 3 months in group 2 and 6 months in group 1, the dose of rHuEPO was modified and adapted to an individual maintenance dose for each patient to achieve a stable Hct between 30% and 32%. The dose ranged from 25 U/kg to 50 U/kg once a week and no significant increase in BP was noted in any of the patients after dose modification.

Discussion

The efficacy of rHuEPO in the amelioration of the anemia of chronic renal failure has been demonstrated in several studies [1–5, 7]. However, approximately 30%–35% of dialysis patients receiving rHuEPO develop hypertension [8, 9]. The development of hypertension in previously normotensive patients, or the worsening of pre-existing hypertension, may require the initiation or modification of antihypertensive medication and may lead to significant morbidity [7, 10–12].

Our data demonstrate that the children at greater risk of developing severe hypertension with high-dose rHuEPO therapy are those with previous hypertension. This is consistent with other studies [7, 10–12]. Although several investigators [7, 11] have shown no correlation between the BP increase and the dose of rHuEPO or the rate of increase of Hct, others [10, 12] showed that the increase in BP was related to the dose of rHuEPO and the rate of Hct rise. In our study, an increase in the mean arterial BP was observed in both groups but severe hypertension occurred only in the patients who were previously hypertensive and received high-dose rHuEPO therapy (150 U/kg per week). Antihypertensive therapy had to be intensified in all of the 8 previously hypertensive patients on high-dose rHuEPO therapy. No such change was required for the patients receiving rHuEPO weekly (50 U/kg per week). In our study, pre-existing hypertension and the dose of rHuEPO seem to

be the most important risk factors for the development or worsening of hypertension in children on CAPD.

We conclude that during rHuEPO treatment careful monitoring of BP is essential for children on CAPD with previous hypertension. In our patients, a clear dose-dependent response was observed but the side effects were also mainly related to the total amount of drug administered. We believe that there is no need for a rapid correction of anemia in children on CAPD with high-dose rHuEPO. Gradual elevation of Hct by weekly administration of rHuEPO is considered optimal for avoiding the development of severe hypertension. Furthermore, weekly therapy is effective, more convenient, and less expensive than thrice weekly therapy.

References

1. Macdougall IC, Cavil I, Davies ME, Hutton RD, Coles GA, Williams JD (1989) Subcutaneous recombinant erythropoietin in the treatment of renal anemia in CAPD patients. Contrib Nephrol 76:219–226
2. Faller B, Slingeneyer A, Waller M, Michel C, Grützmacher P, Müller HP, Barany P, Grabensee B, Issad B, Schmitt H, Meisl F (1993) Daily subcutaneous administration of recombinant human erythropoietin in peritoneal dialysis patients: a European dose-response study. Clin Nephrol 40:168–175
3. Hisano S, Kaku Y, Ueda K, Onoyama K (1992) Human erythropoietin in children undergoing continuous ambulatory peritoneal dialysis. Acta Paediatr Jpn 34:36–41
4. Lui SF, Law CB, Ting SM, Lai KN (1991) Once weekly versus twice weekly subcutaneous administration of recombinant human erythropoietin in patients on continuous ambulatory peritoneal dialysis. Clin Nephrol 36:246–251
5. Kleinman KS, Schweitzer SU, Perdue ST, Bleifer KH, Abels RI (1989) The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function. A double-blind, placebo-controlled trial. Am J Kidney Dis 14:486–495
6. Report of the Second Task Force on Blood Pressure Control in Children (1987) Pediatrics 79:1–25
7. Steffen HM, Brunner R, Müller R, Degenhardt S, Pollok M, Lang R, Baldamus CA (1989) Peripheral hemodynamics, blood viscosity and the renin angiotensin system in hemodialysis patients under therapy with recombinant human erythropoietin. Contrib Nephrol 76:292–298
8. Esbach JW, Abdulhadi MH, Browne JK (1989) Recombinant human erythropoietin in anemic patients with end-stage renal disease. Ann Intern Med 111:992–1000
9. Nissenson AR (1994) Erythropoietin treatment in peritoneal dialysis patients. Perit Dial Int 14 [Suppl 3]:63–68
10. Balaskas EV, Melamed IR, Gypta A, Bargman J, Oreopoulas DG (1992) Influence of erythropoietin on blood pressure in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 13 [Suppl 2]:553–557
11. Samtleben W, Baldamus CA, Bommer J, Fassbinder W, Nonnast-Daniel B, Gurland HJ (1988) Blood pressure changes during treatment with recombinant human erythropoietin. Contrib Nephrol 66:114–122
12. Canadian Erythropoietin Study Group (1991) Effect of recombinant human erythropoietin therapy on blood pressure in hemodialysis patients. Am J Nephrol 11:23–26

Literature abstract

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Detection of hepatitis B virus DNA and RNA in kidneys of HBV-related glomerulonephritis

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Glomerular deposition of hepatitis B virus (HBV) antigens are observed in chronic HBsAg carriers with different glomerulonephritides yet the etiologic role of HBV remains uncertain. We examined the paraffin section of kidney biopsies from 40 chronic HBsAg carriers with membranous nephropathy (MGN), mesangiocapillary glomerulonephritis (MCGN) or IgA nephropathy (IgAN) for HBV DNA and HBV RNA using in situ hybridization (ISH). Glomerular HBV antigens were present in all biopsies by immunofluorescence. HBsAg or HBcAg mRNA was also studied in RNA extracted from frozen renal tissue using a two-step polymerase chain reaction (PCR) following reverse transcription (RT). HBcAg DNA was not easily detected with ISH alone, but was readily found in 31 biopsies (78%) following PCR. HBV DNA was detected mainly in the cytoplasm of proximal tubular epithelia but not in glomerular cells. HBsAg and/or HBcAg mRNA were detected by RT-PCR in extracted RNA from 13 biopsies (33%). The PCR findings were further confirmed by (a) Southern blot hybridization using a cloned HBV probe and (b) absence of PCR product following treating RNA with RNase or omitting the RT. It is plausible that HBV DNA in renal tubules represents endocytosis of HBV DNA in the urinary filtrate and the HBV RNA extracted from kidney biopsies could derive from infiltrating cells bearing HBV RNA. Hence, ISH with specific HBV core gene RNA probe was performed subsequently. HBcAg RNA, localized in the nuclei and cytoplasm of glomerular and tubular cells, was detected in 56%, 20%, and 36% of renal biopsies in chronic HBsAg carriers with MGN, MCGN, and IgAN, respectively. Our findings indicate the presence of viral transcription in glomerular cells and renal tubular epithelia, supporting an etiological role of HBV in some chronic HBsAg carriers who develop coexisting glomerulonephritides.