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The Effect of Subcutaneous Recombinant Human Erythropoietin (r-Hu EPO) in CAPD Patients with Renal Anaemia

Efekt leczenia erytropoetyną (r-Hu EPO) podawaną podskórnie na niedokrwistość u pacjentów leczonych CADO

Several factors may contribute to the pathogenesis of uraemic anaemia but there is general agreement that inadequate secretion of erythropoietin is the main cause (6). Recombinant human erythropoietin (r-Hu EPO) is today widely used in the treatment of patients with renal anaemia.

Initial studies were conducted on patients receiving haemodialysis (HD) using intravenous dosing, and number of reports have confirmed the efficacy and safety of the hormone (3, 4). However, there is still limited information on the use of r-Hu EPO in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). The cost of this treatment was initialy very high. The optimal way of administration of the drug and optimal dosage is still under discussion (2, 13). More studies are needed to optimize treatment from a clinical as well as an economic point of view. We therefore present our result on the efficacy and safety of low dose r-Hu EPO given subcutaneously in th treatment of anemia in CAPD patients.

PATIENTS AND METHODS

We have studied 4 stable patients on CAPD (3 males, 1 female) with a mean age 45 years (range: 34 to 55). Their underlaying renal disease was chronic glomerulonephritis (1 patient), diabetic nephropathy (1 patient), obstructive nephropathy (1 patient) and interstitial nephritis (1 patient). Any other cause than uraemia did not account for the anaemia. None of the patients had clinical peritonitis during the time of studies. All studies were executed in the Nephroloy Clinic of the Medical Academy in Lublin. The informed consent was obtained according to the principles of the Declaration of Helsinki. In our study subcutaneous r-Hu EPO was administered 2 times per week, an inclusion criterion was a stable initial haemoglobin (Hb) concentration below 9 g/dl in the patients.

The starting dose depends on the baseline Hb level, as Hb > 8 gd/dl: 25 u/kg 2 × week, at

Hb < 8 g/dl: 50 U/kg 2 × week. A good guideline for adequate response in an increase of the Hb concentration of 1 g/dl per 4 weeks. If the Hb has increased > 1,2 g/dl, the r-Hu EPO dose has had to be lowered: the change was from 50 U/kg 2 × week to 25 U/kg 2 × week, and from 25 U/kg 2 × week to 15 U/kg 2 × week. If the rise was < 1 g/dl compared with baseline level and Hb was still < 9 g/dl without tending to increase, the dose had to be increased: change from 25 U/kg 2 × week to 50 U/kg 2 × week, and from 50 U/kg 2 × week to 75 U/kg 2 × week. If the Hb was already within the target range and stable, the current dose was then the maintenace dose and had to be reviewed every 4 weeks. If the Hb exceeded 12 g/dl, r-Hu EPO dosing had to be discontinued for 4 weeks until the Hb level had returned to values between 10-12 g/dl, and then restarted at the next lower dose Hb, checking level every week until Hb was stable. The target Hb concentration was 10-12 g/dl. Blood pressure and body temperature were measured before and 15 munutes after each erythropoietin injection. Erythrocyte counts (RBC), Reticulocyte counts, Haemoglobin (Hb), Haematocrit (Ht), Mean Corpuscular Volume (MCV), Leukocyte count (WBC), Leukocyte differential count, were monitored weekly. Plasma urea, creatinine, sodium (Na), potassium (K), total calcium (Ca), phosphorus inorganic (P), albumin, total bilirubin, activity of alkaline phosphate (AP), SGOT, SGPT, serum iron, platelet count and ferritin were checked monthly. Standard laboratory methods were used. Quality of life was assessed only clinically, mainly capacity for work, house-hold activities and social activities. For statistical analysis paired Student's t-test used and p value of < 0,005 was considered significant.

RESULTS

All patients responded to erythropoietin. The change in hemoglobin concentration with treatment is shown in Fig. 1. During r-Hu EPO treatment (after 5 weeks) a significant increase of hemoglobin concentration was observed ($p < 0,05$). Fig. 2 illustrates the changes in hematocrit during r-Hu EPO treatment. During r-Hu EPO treatment (after 5 weeks) a significant increase of hematocrit was observed ($p < 0,05$). Fig. 3 presents the changes in red cell count during r-Hu EPO treatment. There was a significant increase in red cell count ($p < 0,05$). Fig. 4 shows the changes in reticulocyte count. An increase in reticulocyte was seen within one week from the start of the treatment ($p < 0,05$). As was shown in Fig. 5 the mean systolic and diastolic blood pressure was not changed in our CAPD patients treated with r-Hu EPO. There were no significant changes in total white cell or platelet counter over the first 6 months of r-Hu EPO administration. As was shown in this study (Table 1), long term r-Hu EPO treatment did not influence plasma levels of electrolytes (sodium, potassium, calcium, inorganic phosphorus, urea, creatinine, alkaline phosphatase, total protein and albumin. Liver function tests were normal of the beginning and at the end of the study. In the present study, the correction of anaemia was accompanied by a substantial improvement in the quality of life, mainly capacity for work, house-hold activities and social activities. All patients reported great improvement of well-being; their asthenia, fatigue, headache and tachycardia disappeared. A substantial improvement in appetite was reported. Side effects in the study were minimal: 1 patient had myalgia after the first doses of r-Hu EPO but did not require drug withdrawal.

Table 1. Plasma levels of biochemical parameters assessed in CAPD patients treated by r-Hu EPO (Mean ± SD)

	Observation period					
	1	2	3	4	5	6
Urea (mmol/l)	26.5 ± 10	21.6 ± 5.1	23.3 ± 6.7	22.1 ± 3.7	27.3 ± 4.1	24.1 ± 1.1
Creatinine (mmol/l)	963 ±231	979 ±210	980 ±83.4	1003 ±538	1007 ±50	970 ±75
Sodium (mmol/l)	143 ± 1.8	137.2 ± 3.7	141.7 ± 3.6	141 ± 2.1	142 ± 5	141.5 ± 0.5
Calcium (mmol/l)	4.2 ± 0.3	4.7 ± 0.2	4.8 ± 0.7	4.9 ± 0.2	5 ± 0.3	4.2 ± 0.1
Potassium (mmol/l)	5.0 ± 0.4	4.6 ± 0.6	4.7 ± 0.5	5.2 ± 0.2	5.1 ± 1.1	5.1 ± 0.7
Alkaline phosphate	5.9 ± 1.2	5.9 ± 1.4	5.7 ± 0.6	5.9 ± 0.6	6.0 ± 2.2	5.9 ± 1.3
Albumin (g%)	3.6 ± 0.4	3.7 ± 0.3	4.2 ± 0.2	3.7 ± 0.4	3.6 ± 0.5	4 ± 0.1
Platelets count	217 ± 44.7	259 ± 14.4	307,6 ± 8.4	232 ± 31.6	220 ±15	229 ±31.6

DISCUSSION

Our study shows that subcutaneous r-Hu EPO is effective in treating anaemia and maintains and increased haemoglobin concentration in CAPD patients.

In the present study mean initial dose of r-Hu EPO was 62,5 U/kg/week and maintanance dose were between 36,7 to 44,7 U/kg/week. We have shown that the acceptable target haemoglobin concentration can be achieved with considerably lower doses of r-Hu EPO given subcutaeously than those the manufacturers recommended for intravenous administration and at a lower dose than in many previous reports (1, 10, 12, 14). Pharmacokinetic studies of subcutaneous and intravenous r-Hu EPO application indicate a moderate but long-lasting increase of serum r-Hu EPO levels after subcutaneous injection in contrast to a supraphysiological but shorter lasting elevation of serum r-Hu EPO levels after intravenous injection (8, 9).

The extremely high peaks obtained after intravenous r-Hu EPO are not required for its therapeutic efficacy. For this reason, and because r-Hu EPO levels after subcutaneous administration persist longer (3-4 days) than after intravenous injection, it would seem reasonable to recommend the subcutaneous route for treating CAPD and haemodialysis patients with r-Hu EPO. As shown in the present study the mean systolic and diastolic blood pressure was not changed.

In haemodialysis patients treated with intravenous r-Hu EPO, the increase in blood pressure is common and is sometimes associated with seizures, requiring interruption or readjustment of the r-Hu EPO therapy. In the u.s. multicentred study, described by Eschbach et al. (6), 103 out of 330 patients (31%) had an increase in their diastolic blood pressure of greater than 10 mmHg or a requirement for new or additional antihypertensive medication.

Hypertensive problems appear to be greater in patients who have been previously hypertensive and when haemoglobin rises rapidly (7). It seems that higher initial r-Hu EPO doses may be accompanied by increased hypertension in CAPD patients and that this may be prevented by a lower initial dose and lower rate of increase in haemoglobin and haematocrit. Howerver, close observation of blood pressure is clearly improtant during r-Hu EPO therapy in CAPD patients. Side effects in our study were minimal. One patient had myalgia after the first seven doses but this disappeared as treatment was continued.

It has been observed in some haemodialysis patients that predialysis serum potassium increased during treatment with r-Hu EPO which almost universally required the regular use of cationic exchange resins during the whole period of follow-up (5). No change in serum urea, cratinine, potassium and phosphate was observed in our CAPD patients which suggested that the efficacy of peritoneal transport was not reduced by the increase in hematocrit. Steinhauer et al. (11) reported an increase in net ultrafiltration volume during r-Hu EPO treatment. We found no significant changes in ultrafiltration volumes.

In the present study the correction of anemia was accompanied by a substantial improvement in patients rehabilitation and quality of life which was maintaned over the period of the study.

Angina pectoris which had been reported occasionally by two patients before the study, no longer occurred after correction of the anaemia. These results were obtained from a relatively small number of patients but we conclude that subcutaneous low dose r-Hu EPO has been an effective and well-tolerated treatment for renal anaemia in CAPD patients.

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STRESZCZENIE

Badania przeprowadzono u czterech pacjentów leczonych CADO. Erytropoetynę (r-Hu EPO) podawano podskórnie 2 razy w tygodniu przez okres 6 miesięcy. Stężenie hemoglobiny utrzymywano w granicach 10-12 g/dl. Średnia początkowa dawka r-Hu EPO wynosiła 62,5 U/kg/tydzień, dawka podtrzymująca wahała się od 36,7 do 44,7 U/kg/tydzień. U wszystkich pacjentów obserwowano istotny statystycznie wzrost stężenia hemoglobiny ($p < 0,05$), hematokrytu ($p < 0,05$) oraz poprawę stanu ogólnego. W czasie prowadzonego leczenia nie obserwowano wzrostu ciśnienia tętniczego krwi, stężenia mocznika i kreatyniny oraz zaburzeń elektrolitowych.

Prowadzone badania wykazały, że leczenie małymi dawkami r-Hu EPO podawanej podskórnie, korygowało niedokrwistość, nie wywołując objawów ubocznych.

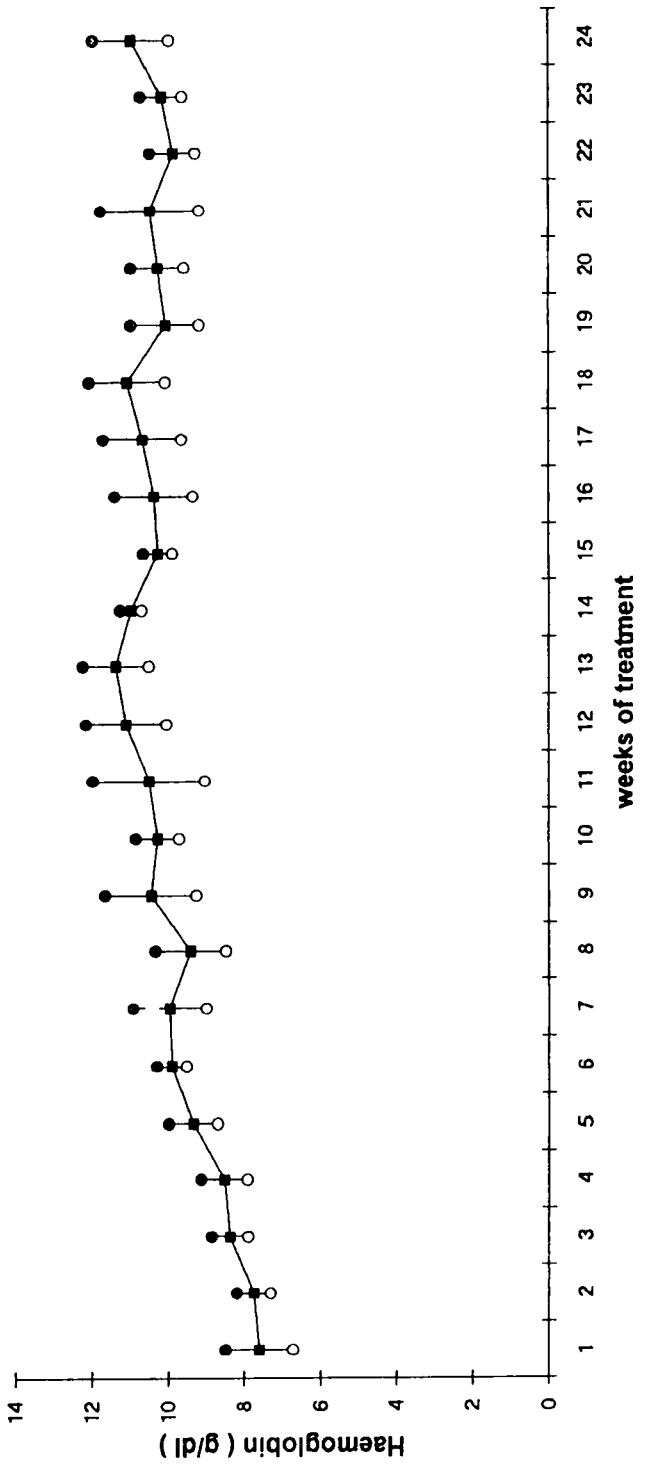

Fig. 1. Effect of Recombinant Human Erythropoietin (r-Hu EPO) on Haemoglobin in CAPD Patients with Anemia (mean ±SD)

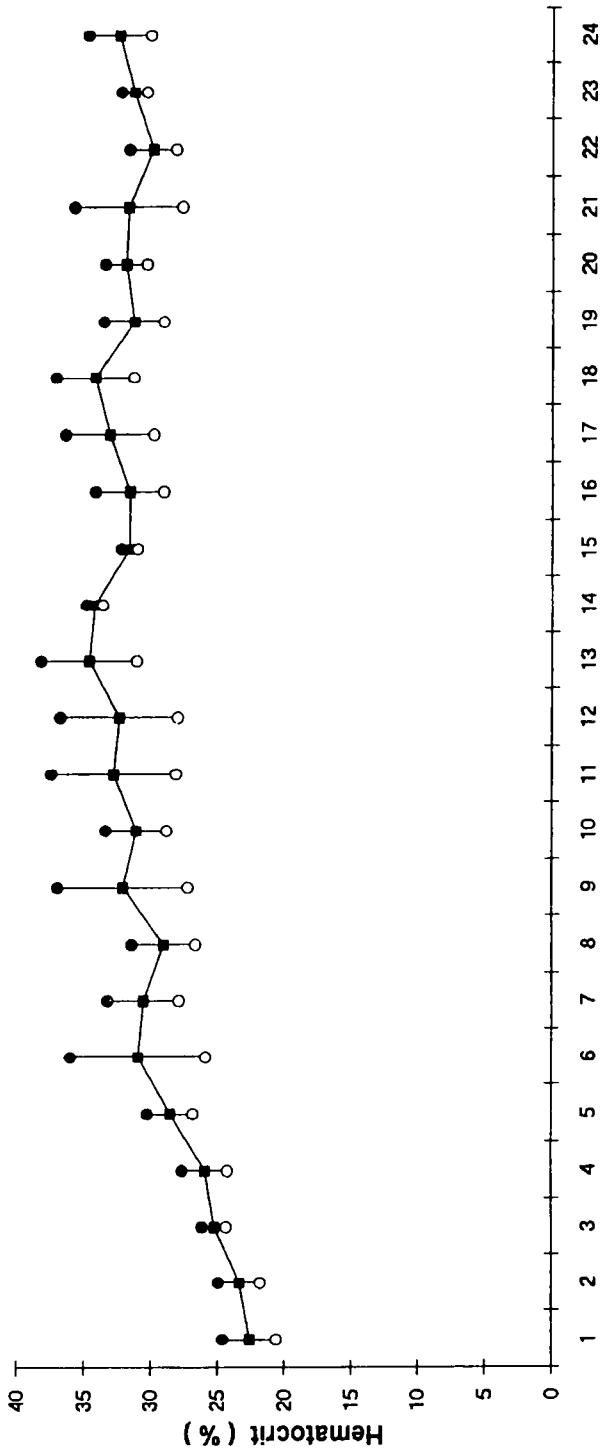

Fig. 2. Effect of Recombinant Human Erythropoietin (r-Hu EPO) on Hematocrit in CAPD Patients with Anemia (mean ±SD)

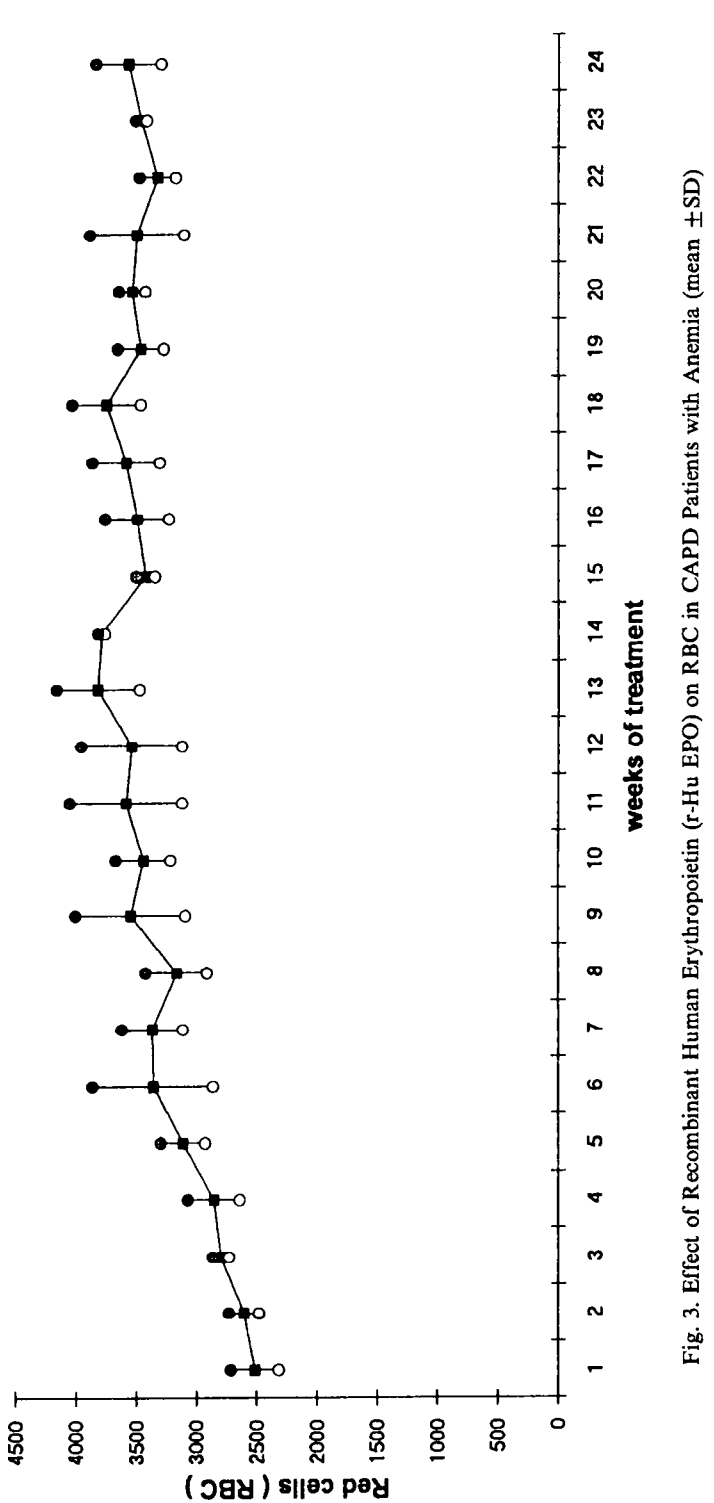

Fig. 3. Effect of Recombinant Human Erythropoietin (r-Hu EPO) on RBC in CAPD Patients with Anemia (mean ±SD)

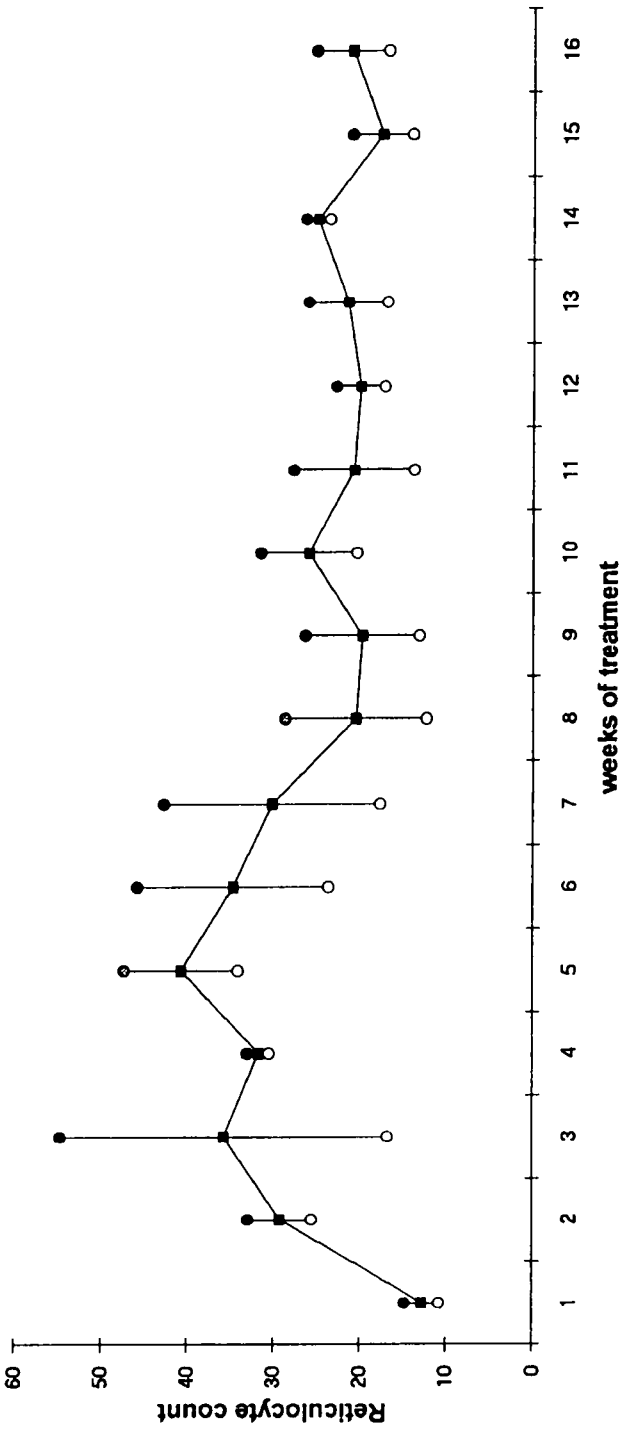

Fig. 4. Effect of Recombinant Human Erythropoietin (r-Hu EPO) on Reticulocyte in CAPD Patients with Anemia (mean ±SD)

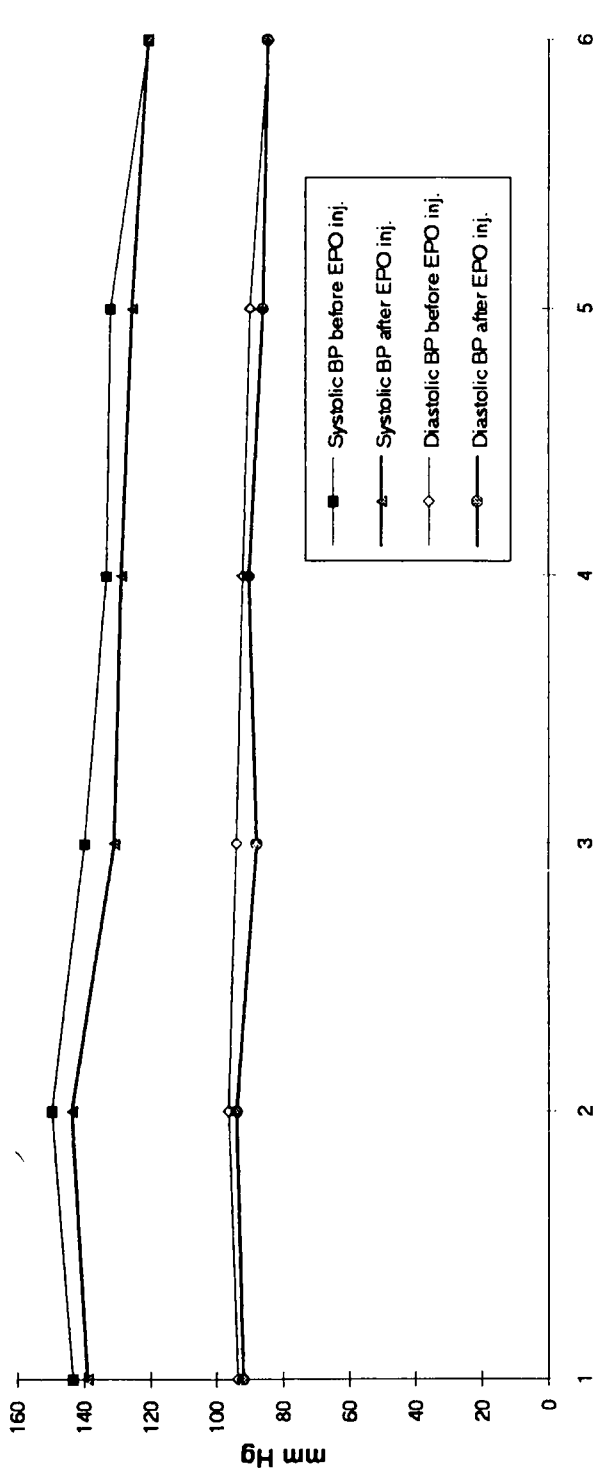

Fig. 5. Systolic and Diastolic Blood Pressure in 4 CAPD Patients Treated with r-Hu EPO (mean)

EPREX

... ŚWIATOWY LIDER

Ludzka rekombinowana erytropoetyna

r-Hu EPO

PRZEŁOM W LECZENIU NIEDOKRWISTOŚCI