

INTRAPERITONEAL ADMINISTRATION OF RECOMBINANT HUMAN ERYTHROPOIETIN

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Objective: To determine the efficacy and safety of intraperitoneal administration of recombinant human erythropoietin (rHuEPO) in continuous ambulatory peritoneal dialysis (CAPD) patients compared to subcutaneous rHuEPO.

Design: Prospective analysis of an open, nonrandomized investigation.

Setting: Outpatient CAPD clinics in two university hospitals.

Patients: Nine adult CAPD patients receiving rHuEPO intraperitoneally and 8 patients receiving rHuEPO subcutaneously.

Intervention: One hundred units of rHuEPO per kilogram of body weight were administered three times a week for 8 weeks or until the target hematocrit of 35% was reached. Thereafter, dosages of rHuEPO were adjusted for response. Intraperitoneal rHuEPO was administered in 1 L of dialysis solution during the night.

Measurements: Efficacy was assessed by measuring the increase in hemoglobin. Tolerance was assessed by monitoring side effects.

Results: In the first 8 weeks of treatment hemoglobin concentration increased from 64.5±12.9 g/L to 98.3±16.1 g/L ($p<0.0005$) in the intra peritoneally treated group. In the subcutaneously treated group hemoglobin increased significantly faster ($p<0.05$) from 72.5±4.8 g/L to 119.2±11.3 g/L ($p<0.0005$) in the same period. Antihypertensive medication had to be increased or instituted in most of the patients in both groups. The incidence of peritonitis in the intraperitoneally treated group was not increased when compared to the pretreatment incidence.

Conclusions: Subcutaneously administered rHuEPO is superior to intraperitoneally administered rHuEPO with regard to the required dosages. However, the results of this study show that intraperitoneal administration of rHuEPO might be a convenient and safe alternative when subcutaneous administration is undesirable.

KEY WORDS: Erythropoietin; intraperitoneal administration; anemia.

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In end-stage renal failure most patients have a marked hypoproliferative anemia, which is only slightly affected by dialysis treatment. In patients treated with continuous ambulatory peritoneal dialysis (CAPD), hemoglobin has been reported to be higher than in hemodialysis (HD) patients. The values increase particularly during the first months of CAPD (1-11). In addition to better control of overhydration and increased red cell survival time (12,13), improved erythropoietin effectiveness may be responsible for the increase in red cell mass (5,9,12). These phenomena have been attributed to better removal of middle molecule uremic toxins that affect erythropoietin effectiveness and red cell survival time (3,8,14,15). Increasing erythropoietin production (8,16) and improved protein metabolism (17) might also be important. The relationship between the degree of anemia and *in vitro* inhibition of erythropoiesis by sera of CAPD and HD patients is still controversial (14,18,19). Although CAPD patients seem to have higher erythropoietin values than patients on HD (10,11), no consistent increase of erythropoietin values during therapy has been observed (4,9,18,20). In addition, no strong correlation has been found between serum erythropoietin values and hematocrit in CAPD patients (3,10,11,15). Since erythropoietin values relative to hematocrit are still inappropriately low, the primary cause of the anemia is now considered to be a relative deficiency of erythropoietin production.

Recombinant human erythropoietin (rHuEPO) has been proven to be an effective treatment for the anemia of chronic renal failure when given intravenously to hemodialysis patients (21,22). However, intravenous (IV) administration of rHuEPO, two or three times a week, would be inconvenient in CAPD outpatients. Subcutaneous (SC) administration has been shown to be the most convenient and cost-effective alternative. But subcutaneous administration in children, in particular, can cause considerable psychological distress. Therefore, we carried out a feasibility study to establish the efficacy and the clinical safety of multiple doses of rHuEPO after intraperitoneal administration compared with subcutaneous administration in patients with end-stage

renal failure treated with CAPD.

PATIENTS AND METHODS

Twenty CAPD outpatients eligible for rHuEPO therapy were included in the study after having given informed consent. Two patients were excluded from evaluation because they received a kidney transplant in the first week of the study. One patient in the intraperitoneally treated group was excluded because of recurrent severe menorrhagic bleeding from the start of the study. The remaining 17 patients received rHuEPO either intraperitoneally (n=9) or subcutaneously (n=8). Their median age was 33 years (range 19-70), and the median duration on CAPD was 26 months (range 5-45). None of the patients had diabetes mellitus. Twelve patients were female. Between the two groups no significant differences were found for baseline hematological values, age, cause of renal failure, duration on CAPD, and sex distribution.

All patients had anemia of chronic renal failure with hemoglobin ranging from 50.0-83.8 g/L and hematocrit from 14%-25%. Three intraperitoneally treated patients received regular blood transfusions before rHuEPO therapy. Three of the 8 patients in the SC group and 3 of the 9 patients in the IP group were treated for hypertension prior to rHuEPO treatment. Oral iron supplementation was instituted when serum ferritin values were below 200 $\mu\text{g/L}$. The study protocol was approved by the local Hospital Ethics Committees.

Prior to participation in the study the patients practiced self-administration with a placebo. After a 2-week period of baseline measurements, all patients administered 100 units of rHuEPO (Boehringer Mannheim GmbH, Mannheim, Federal Republic of Germany) per kilogram of body weight (U/kg) per injection, three times a week for 8 weeks or until the hematocrit exceeded the target value of 35%. After this period the dosages of rHuEPO were adjusted for response, at least every 4 weeks. Dose adjustments were made in steps of 25 U/kg per injection. All dosages were rounded off towards the nearest 1000 U. When the hematocrit exceeded 40%, rHuEPO was withheld until the hematocrit had decreased to below the target value. When severe hypertension occurred, no rHuEPO was given until the blood pressure was under control. IP administration was replaced by SC rHuEPO when peritonitis occurred.

Before study entry all patients performed four 2 or 1.5-L exchanges per 24 hours. In the patients who administered rHuEPO intraperitoneally, the volume of the night bag was reduced to 1 L (1.5% glucose) three times a week. Immediately before infusion rHuEPO was dissolved into at least a 10 mL volume and injected slowly into the bag via the additional tube devised for sampling and injection. The patients used needles that were long enough to inject the solution directly into the bag, and ensured that no fluid remained in the tube. The dialysis fluid

was not mixed before infusion to prevent adherence of rHuEPO to the bag. SC injections of rHuEPO were given in the thighs.

The patients visited the outpatient clinic twice a week in the correction phase and once a week thereafter. At these intervals hemoglobin, hematocrit, and blood cell counts were done, and blood pressure was measured. Serum chemistry was monitored every 2 weeks.

To prove that rHuEPO is stable in various dialysate glucose solutions, studies in the laboratories of Boehringer Mannheim GmbH (Mannheim, Federal Republic of Germany) showed that there was no significant progressive loss of biological activity (mouse spleen assay) of rHuEPO incubated at 37°C in 1.5%, 2.3%, and 4.25% (commercially available) glucose solutions for periods up to 20 hours. In these solutions no aggregates of the hormone could be demonstrated using high-performance liquid chromatography (data not shown). Due to technical problems concerning the radioimmunoassay (RIA) based determination of rHuEPO in peritoneal dialysis fluids, we were not able to calculate recovery rates of rHuEPO from these fluids in patients.

Differences from baseline values within the groups were evaluated using the Student's t-test for paired data. Comparison of several groups of data was done with analysis of variance. A p value of less than 0.05 was considered significant. Unless otherwise stated, all values are expressed as mean plus/minus standard deviation (SD).

RESULTS

In the subcutaneously treated group, 1 patient left the study at week 18, because rHuEPO had to be withheld due to severe hypertension. In 2 more patients rHuEPO therapy was stopped for a prolonged period of time due to high hematocrits after week 18. Another patient discontinued rHuEPO treatment at week 10, when his hemoglobin had reached 135.4 g/L. One patient received a kidney transplant at week 6 of the study. In 1 patient CAPD was replaced by hemodialysis after abdominal surgery in week 18. The remaining 2 patients completed the 26 weeks' follow-up. In 2 patients IP administration of rHuEPO was replaced by SC rHuEPO in week 22 after peritonitis had occurred.

A continuous rise in hemoglobin and hematocrit occurred within 2 weeks of beginning rHuEPO (Figure 1). Mean hemoglobin in the IP group increased from 64.5 \pm 12.9 g/L to 98.3 \pm 16.1 g/L ($p<0.0005$) after 8 weeks of treatment. In the SC group hemoglobin increased from 72.5 \pm 4.8 g/L to 119.2 \pm 11.3 g/L ($p<0.0005$) in the same period. Hematocrit increased from 19 \pm 4% to 29 \pm 5% ($p<0.0005$) in the IP group, and from 22 \pm 1% to 37 \pm 4% ($p<0.0005$) with SC rHuEPO. The rate of increase in hemoglobin and hematocrit in the subcutaneously treated group was twice the rate in the intraperitoneally treated group ($p<0.05$). In the SC

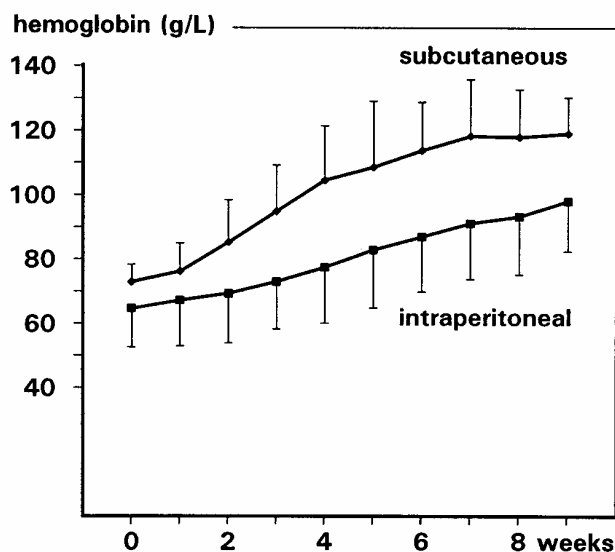


Figure 1 — Mean (SD) hemoglobin values during the correction phase in CAPD patients treated with intraperitoneal erythropoietin (n=9) or subcutaneous erythropoietin (n=8).

group a 50% increase in hematocrit was reached after 4.5 weeks, whereas an equal increase in the IP group occurred after 9 weeks of treatment. In the maintenance phase the mean IP rHuEPO dose was 85 ± 45 U/kg/injection (range 40-130 U/kg/injection, n=9), three times a week.

In the intraperitoneally treated group mean platelet counts increased significantly, from $227 \pm 50 \times 10^9/L$ to a maximum of $292 \pm 55 \times 10^9/L$ ($p < 0.02$) after 7 weeks of treatment. No persistent change from base

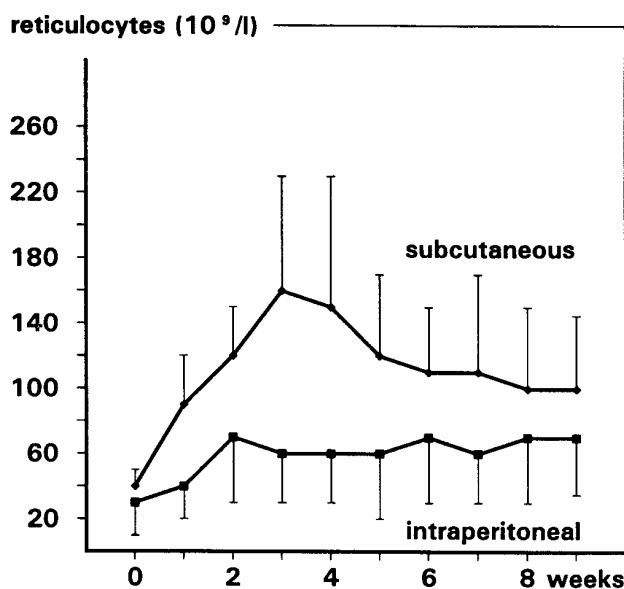


Figure 2 — Mean (SD) reticulocyte counts during the correction phase in CAPD patients treated with intraperitoneal erythropoietin (n=9) or subcutaneous erythropoietin (n=8).

line platelet counts ($225 \pm 60 \times 10^9/L$) was observed in the SC group. An increase ($p < 0.02$) in the mean reticulocyte counts was seen after 2 weeks of treatment in the IP group, and after 1 week in the SC group (Figure 2). During the first 6 weeks of treatment, mean reticulocyte counts were significantly higher in the SC group when compared to the intraperitoneally treated group. There was no significant change of total leukocyte counts. Prior to rHuEPO therapy median ferritin concentrations were significantly higher in the IP group. Serum ferritin values decreased significantly in 6 patients in each treatment group.

During 210 treatment weeks in the intraperitoneally treated group, 6 episodes of peritonitis occurred in 5 patients. In the SC group 2 episodes of peritonitis occurred in 1 patient, whereas the followup in this group was 140 treatment weeks. In equally long periods before rHuEPO treatment, 5 episodes of peritonitis occurred in 3 patients in the IP group, and 5 episodes in 2 patients in the SC group.

Median systolic and diastolic blood pressure did not change throughout the study. However, increased antihypertensive therapy was required in all 3 patients in the IP group and 2 of the 3 patients in the SC group who were on antihypertensive medication prior to the study. In 4 intraperitoneally treated patients and 2 subcutaneously treated patients antihypertensive medication had to be instituted.

SC rHuEPO was well tolerated and did not cause local pain or side effects. All patients mentioned an increase in well-being and exercise tolerance. Blood transfusions were no longer required by the patients who needed regular blood transfusions prior to rHuEPO therapy. In 2 female intraperitoneally treated patients menstrual bleedings that were irregular prior to rHuEPO therapy became regular and more abundant during the treatment period. In 1 other patient who had secondary amenorrhea, normal menstruations resumed within one month of beginning IP rHuEPO therapy. No significant changes in clinical chemistry parameters were observed.

DISCUSSION

It has been shown recently that the mean bioavailability of SC rHuEPO ranged from 18%-49% of that after IV administration (23-25). These investigations also revealed that after IP administration the mean bioavailability was even lower, ranging from 3%-7%. These studies suggested that SC and especially IP rHuEPO would not be effective therapeutic approaches. However, clinical studies demonstrated that SC rHuEPO allowed for even lower dosages than IV rHuEPO to obtain the same therapeutic effect (26).

The efficacy of SC rHuEPO in CAPD patients and in patients treated with continuous cyclic peritoneal dialysis has now become established (27-31). The results of the present study show that IP rHuEPO is also effective. However, with SC rHuEPO the rate of

correction of the anemia was twicethatofIPrHuEPO. Three female patients in the IP group suffered from an important increase in menstrual blood loss during the correction phase of the anemia. Although serum ferritin values in the IP group were higher than in the subcutaneously treated group, it cannot be excluded that these blood losses influenced the rate of increase in hematocrit. Recently a study in children treated with CAPD showed similar results when IP rHuEPO was administered three times a week in a 20 mL/kg overnight volume (32).

The above-mentioned pharmacokinetic studies with IP rHuEPO were done with an injection of rHuEPO into 2-L dialysis bags, with dwell times ranging from 4-12 hours. The results were in contrast with the 60% absorption of 125I -erythropoietin

from the peritoneal cavity in the uremic rabbit after a 6-hour dwell (33). Absorption from the dry peritoneal cavity after 24 hours even reached 97%. It is not known by which mechanism rHuEPO (molecular weight 34000 dalton) is absorbed from the peritoneal cavity. However, it has been recently demonstrated that the disappearance of intraperitoneally administered macromolecular solutes takes place mainly by lymphatic absorption. In CAPD patients absorption rates of about 1.5 mL/minute are found (34-37). Therefore, theoretically one would expect that the bioavailability of a fixed dose of IPrHuEPO would increase with longer dwell times and with lower intraperitoneal dialysate volumes. In the ideal situation IP rHuEPO should then be administered undiluted. Since in many outpatients changes in the daytime dwell schedule are inconvenient, we preferred to reduce the overnight volume to 1 L three times a week in this study. This did not interfere significantly with solute clearances as judged from the unchanged clinical chemistry data.

Several reasons other than the return of unused rHuEPO in dialysate effluent might explain the higher dosage requirements of IPrHuEPO. IP degradation of rHuEPO was excluded by *in vitro* studies as mentioned in the patients and methods section. Adsorption of rHuEPO onto the polyvinyl chloride of the fluid containers and connecting tubes also might reduce the amount of rHuEPO available (38). However, when the rHuEPO solution is slowly injected into the bag, ensuring that no fluid remains in the injection tube connected to the bag, mixing with the rather viscous CAPD dialysate will only occur to a small extent. Immediate infusion of the dialysate will minimize the adherence of rHuEPO to the bag. Analysis by bioassay of a limited number of dialysate samples taken immediately after infusion of the dialysate showed no significant differences in rHuEPO concentrations compared to the predicted values, when IP residual volumes were taken into account (data not shown). However, more precise measurements await the solution of technical problems associated with the RIA determination of rHuEPO in dialysis fluids.

In some studies with IV rHuEPO, increases in

platelet counts were observed (39-41). This was not observed using lower dosages of SC rHuEPO. We were surprised to see that in the IP group, in contrast to the SC group, mean platelet counts increased significantly, despite a lower rate of increase in hematocrit and significantly lower reticulocyte counts. However, in none of the patients did the platelet counts exceed the upper limit of normal.

Increases in antihypertensive drugs prescribed or institution of antihypertensive therapy in previously normotensive patients occurred in both treatment groups, independent of the rate of increase in hematocrit. The overall incidence of peritonitis during the study did not differ from the pretreatment period in the intraperitoneally treated group. Our experience suggests that with careful training the additional risk of peritonitis with IP administration of rHuEPO is minimized, similar to the results with IP administration of insulin in diabetics (42).

Although SC rHuEPO is superior for the treatment of anemia associated with chronic renal failure, the results of this study show that IPrHuEPO might be a convenient and safe alternative when SC administration is undesirable. Moreover, it can be concluded that standard descriptive pharmacokinetics alone are not appropriate to predict the biological response to rHuEPO. Further improvement of the IP efficacy might be achieved by reducing the volume in which rHuEPO is administered (33).

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