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Stepwise-Decreasing Erythropoietin Dosing Schedule for the Treatment of Anemia in Dialyzed Patients

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ABSTRACT

Recombinant human erythropoietin (rHuEpo) is very useful for the treatment of anemia in dialyzed patients. However, not all patients response similarly to rHuEpo and there is still no consensus on the optimal rHuEpo dose and dosing schedule. In this study we use a stepwise-decreasing rHuEpo dosing schedule to treat the anemia of dialyzed uremic patients. Thirteen dialyzed patients with hematocrit < 23 vol % were chosen for the 12-week's study. Hemoglobin and hematocrit increased significantly ($p < 0.005$) at 4th week. The mean hematocrit before treatment was 20.7 vol% and increase to 30.4 vol% at the end of study. No significant changes in MCV, leukocytes, platelets, BUN, serum creatinine and electrolytes were noted. Serum iron and ferritin levels decreased after therapy. All patients showed sense of well-being, increase in appetite and exercise tolerance. Elevated blood pressure requiring increased dose of antihypertensive drugs occurred in 2 patients. Dialyzer tubing cloting occurred in one patient, but no A-V fistula thrombosis was observed. One patient suffered from insomnia and 2 patients suffered from flu-like symptoms at the begining of treatment. In conclusion, this method is convenient, effective and safe for the treatment of anemia in dialyzed uremic patients.

Keywords: Erythropoietin, Anemia, Hemodialysis.

Recombinant human erythropoietin (rHuEpo, Epogin) is very useful for the treatment of anemia in dialyzed patients[1-8]. However, not all patients response similarly to rHuEpo therapy and there is still no concensus on the optimal rHuEpo dose, frequency and route of administration. Recent reports revealed that the rate, but not the magnitude, of increase in hematocrit is dose dependent[1,7,8]. In most clinical studies the doses of rHuEpo were not reduced until the target hemoglobin concentrations were reached[1-8]. In this study we use a stepwise-

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decreasing rHuEpo dosing schedule for the treatment of anemia in the uremic patients on maintenance hemodialysis.

PATIENTS AND METHODS

Thirteen patients with end-stage renal disease on maintenance hemodialysis were chosen for the study. Each patient was dialyzed for 4-4.5 hours thrice weekly with cellulose membrane using either acetate or bicarbonate dialysate. The patients included 8 men and 5 women, whose mean age was 55.3 ± 4.9 years (range, 30 to 76 years). The average time on hemodialysis was 46.3 ± 12.7 months, with a range from 3 months to 12 years. The patients were chosen to receive Epogin therapy if they met all the following criteria: hematocrit less than 23 vol%, no active seizure disorder or uncontrolled hypertension and no iron deficiency before therapy.

STUDY DESIGN

As shown in figure 1, in the first 4 weeks each patient received 3000 IU Epogin (Chugai Pharmaceutical Co. Tokyo, Japan) directly into their venous return line at the end of dialysis three times weekly. In the second 4 weeks, Epogin dose was reduced to 3000 IU twice weekly for those who showed > 3 vol% increase in hematocrit (Responder) and dose remained the same for those who showed < 3 vol% increase in hematocrit or had no response (Non-responder). In the third 4 weeks, Epogin dose was further reduced to 1500 IU thrice weekly for

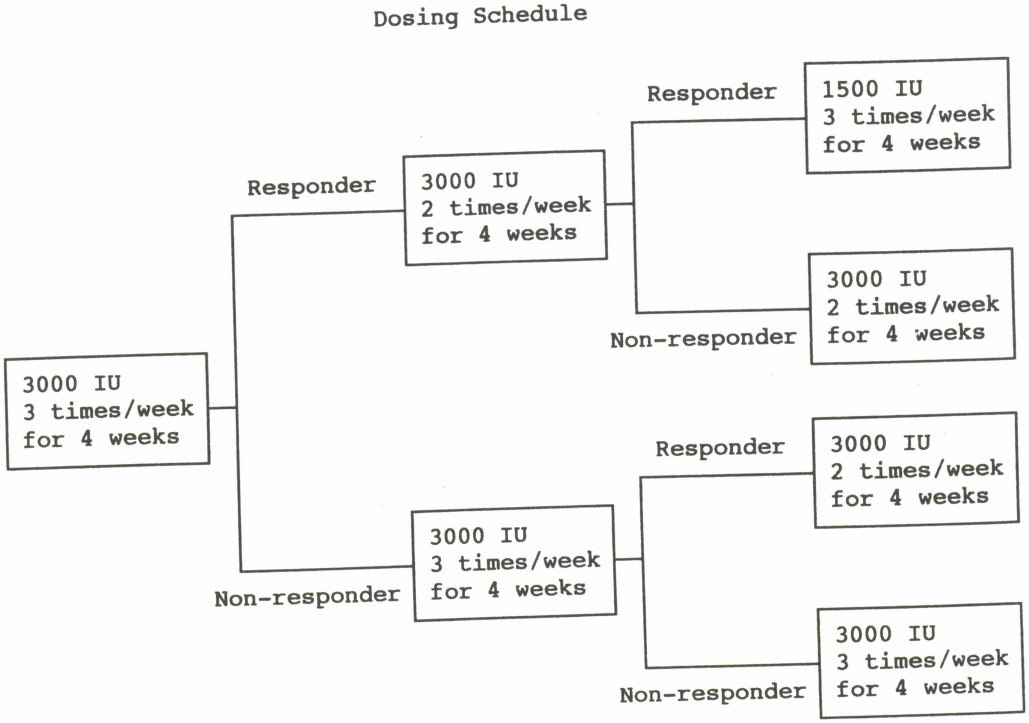

Fig. 1. Stepwise-decreasing Epogin dosing schedule.

responders. Eleven patients complete 12-weeks treatment. Two patients were excluded, one died of disease unrelated to treatment, the other due to irregular frequency of drug administration.

Hemoglobin, hematocrit, RBC, WBC, platelet, and MCV were measured every 4 weeks or more frequently if indicated by a rapid change. A complete predialysis serum chemistry profile and serum iron, ferritin were assessed before Epogin treatment and every 4 weeks after treatment. Blood pressure was measured before and after each dialysis treatment with a mercury manometer. All blood transfusions, clotted dialyzers, thrombosed accesses, seizures, dry weight changes, interdialysis weight gain, and side effects of treatment were noted and recorded. Some patients received oral iron supplement to maintain serum ferritin levels above 100 μg/L. Patients were transfused only when symptoms of anemia were noted.

Data collected are presented as mean ± SEM compared with paired Student's t test. Correlation is determined by linear regression. A p value less than 0.05 was considered significant.

RESULTS

The mean weekly Epogin doses per kilogram body weight were 167.9 ± 5.9 IU, 122.7 ± 9.8 IU and 100.5 ± 10.9 IU, for the first, second and third 4 weeks, respectively. Within 4 weeks of therapy, there was a significant increase ($p < 0.005$) in mean hematocrit and hemoglobin concentrations (Figure 2 and 3). The mean hematocrit before treatment began was 20.7 vol% and increased to 30.4 vol% at the end of study. The greatest increase in mean hematocrit occurred during the first 8 weeks and remained stable thereafter. Nine of 11 patients had an increase in their hematocrit of 6 vol% or greater, 6 of 11 patients had an increase of hematocrit more than 10 vol% (figure 4). Magnitude of the response to therapy did not correlate with rHuEpo dose or ferritin level. Five of the 11 patients required blood transfusion before Epogin therapy. They were transfused a total of 19 units packed RBC in the three months preceding rHuEpo, an average of 0.57 unit per patient per month. Only one patient failed to response to Epogin therapy and had received 2 units of packed RBC transfusion due to symtoms of anemia at the end of 4th week, and no patient required transfusion thereafter, representing a 0.06 units per patient per month. No significant changes in MCV, leukocytes, plateletes, BUN, creatinine and electrolytes were noted. Serum iron level decreased significantly from 124 ± 18.9 μg/dl to 77.3 ± 18.2 μg/dl at the end of study ($p < 0.05$). Serum ferritin level also decreased from 1645.2 ± 569.9 to 1454.5 ± 632.9 μg/L after treatment but did not reach a statistical significance. All patients showed sense of well-being, increase in appetite and exercise tolerance. Six patients were receiving oral antihypertensive drugs at the initiation of Epogin therapy. Elevated blood pressure requiring increased dose of antihypertensive drugs occurred in 2 patients. Dialysis tubing clotting was noted in one patient, but no A-V fistula thrombosis was observed. One patient suffered from insomnia and 2 patients suffered from flu-like symptoms at the beginning of treatment. One patient had acute pulmonary edema due to execessive fluid and food intake after Epogin therapy. No patient experienced seizure during the course of study.

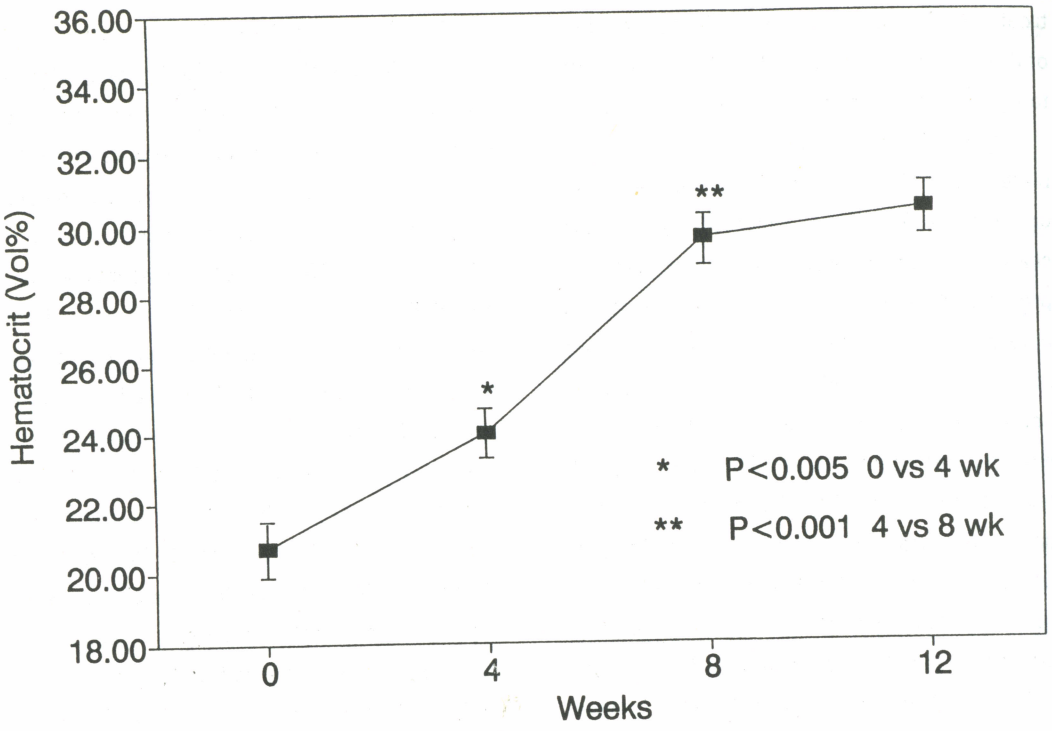

Fig. 2. The response of hematocrit to Epogin treatment.

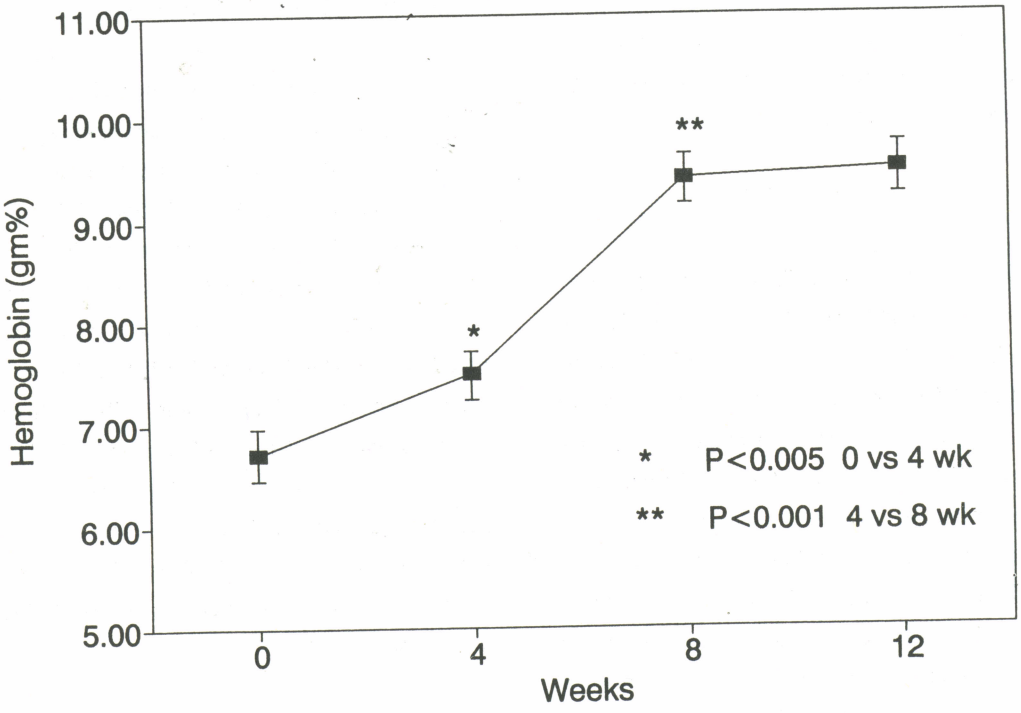

Fig. 3. The response of hemoglobin to Epogin treatment.

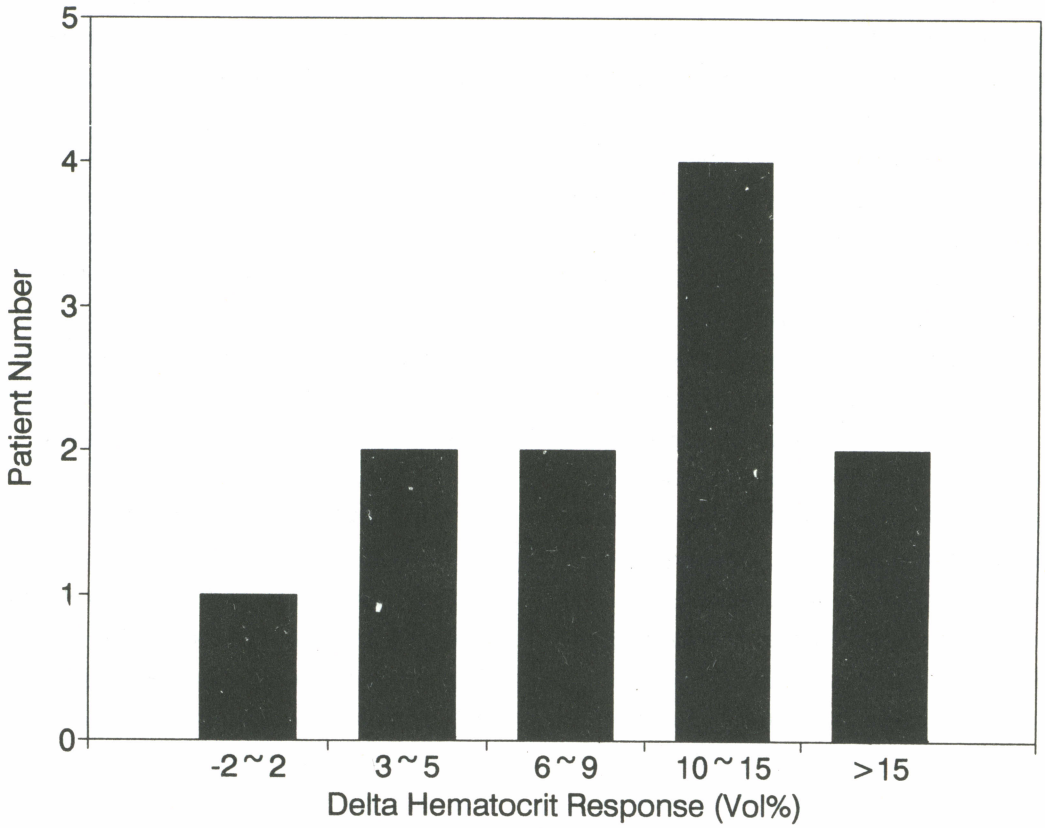

Fig. 4. Frequency and magnitude of the hematocrit response to Epogin.

DISCUSSION

The results of this study indicate that rHuEpo is effective and safe for the treatment of anemia of end stage renal disease. The administration of rHuEpo in stepwise-decrease manner caused a steady rise in hemoglobin concentration; the magnitude of response did not correlate with rHuEpo dose. Eschbach et al. demonstrated that the rate, not the magnitude, of increase in hematocrit is dose dependent[1]. Our results are consistent with this concept. All patients showed an increase in hemoglobin and hematocrit or reduction in transfusion requirement. Therefore, the need of continuous packed red cell transfusions can be eliminated for responders. Serum iron and ferritin level decreased during rHuEpo therapy. Since iron is essential for erythropoiesis, adequate iron store are required to optimized the erythroid response to rHuEpo. Therefore, it is necessary to give suplemental oral or parenteral iron for patients with decreased iron store[3-8,9].

There have been many reports describing elevation of blood pressure followed by rHuEpo therapy[3-8,10-12]. In our study 2 of the 11 patients showed elevation of blood pressure requiring increased dose of antihypertensive drugs. No uncontrollable hypertension or hypertensive encephalopathy was observed. The increase in blood pressure is believed to be

related to the greater blood viscosity due to increasing hematocrit[10-12]. Other works suggest that an increase in peripheral resistance after correction of anemia or the effect of rHuEpo itself on blood pressure may cause an increase in blood pressure[7,12]. Thus, it is reasonable to decrease rHuEpo dose in stepwise manner for those patients who showed good response after the treatment.

Increased incidence of vascular accesses thrombosis, dialyzer or blood line clotting has been reported[3,13]. One of our patients had dialysis tubing clotting once during the course of treatment. Heparin doses have been increased at the initiation of therapy for the prevention of A-V fistula clotting in some reports[3,4,8,13]. Only one of our patients required increased heparin dose.

Serum chemistries measured every four weeks did not change during the 12-week's observation. Because the diaylylsis condition did not change, our data indicate that dialysis efficacy did not decrease during the course of treatment. Hyperkalemia and hyperphosphatemia have been reported[3,4]. Our data did not reveal such findings, maybe because the level of hematocrit achieved in our study was less than that reported in these reports. However, one of our patients showed increased appetite after therapy and suffered from acute pulmonary edema due to excessive fluid and food intake. Therefore, it is very important to instruck the patients to keep their usual diet habit and interdialysis weight gain.

Most of our patients showed good tolerance to the rHuEpo therapy. One patient suffered from insomnia and 2 patients suffered from flu-like symptoms at the beginning of therapy. The adverse effects subsided gradually without any specific treatment. All patients showed sense of well-being, improved appetite, exercise tolerance and physical performance after correction of anemia.

We concluded that stepwise-decreasing rHuEpo dosing schedule is a convenient, effective and safe method for the treatment of anemia in uremic patients on maintenance hemodialysis. However, further studies are needed to confirm the validity of this method and to find the optimal rHuEpo dose and dosing schedule for long term maintenance therapy.

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紅血球生成素梯階式減量法治療透析病人的貧血

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人工合成紅血球生成素治療透析病人的貧血非常有用。然而，並非所有的病人對人工合成紅血球生成素治療的反應都一致。目前對於人工合成紅血球生成素的最佳的劑量和用法仍然還未有一致的意見。本研究是用紅血球生成素梯階式減量法來治療透析尿毒病人的貧血。本研究選擇 13 位血容比小於 23 vol%的血液透析病人做爲期 12 週的治療。血紅素和血容比在第四週時達有意義的增加 ($p<0.005$)。治療前平均血容比爲 20.7 vol%，治療結束時增加到 30.4 vol%，平均血球容積，白血球，血小板，血中尿素氮，肌酐酸和電解質並無顯著的變化。治療後血清鐵和血鐵素濃度下降。所有的病人都覺得精神變佳，食慾和運動耐力增加。二位病人因血壓增高需增加降壓藥的劑量。一位病人發生透析管栓塞，但並無靜脈瘻管栓塞。一位病人治療初期有失眠症，二位病人有類似感冒的症狀。

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