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Neocytolysis Contributes to the Anemia of Renal Disease

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Abstract

Neocytolysis is a recently described physiologic process effecting selective hemolysis of young red blood cells in circumstances of plethora. Erythropoietin depression appears to initiate the process, providing rationale to investigate its contributions to the anemia of renal disease. When erythropoietin therapy was withheld, four of five stable hemodialysis patients demonstrated ^{51}Cr red cell survival patterns indicative of neocytolysis--red cell survival was short in the first 9 days, then normalized. Two of these patients received oral ^{13}C-glycine and ^{15}N-glycine and showed pathologic enrichment of stool porphyrins by the most recently ingested isotope when EPO therapy was held. This confirms selective hemolysis of newly-released red cells. (One patient had chronic hemolysis by isotope studies of blood and stool.) Thus, neocytolysis can contribute to the anemia of renal disease and explains some unresolved issues about such anemia. One implication is the prediction that intravenous bolus erythropoietin therapy is metabolically and economically inefficient compared to lower doses given more frequently subcutaneously.

Introduction

We have uncovered a physiologic process that selectively hemolyzes the youngest circulating red blood cells in situations of red cell excess and have named this process "neocytolysis."[1] Neocytolysis became manifest while studying mechanisms underlying "spaceflight anemia," an adaptation of astronauts to acute plethora in microgravity.[2] Observations on individuals acclimated to high altitude who descend to sea level also suggest neocytolysis, and we are actively extending these observations to further elucidate the process.[3-4] Neocytolysis occurs in situations where erythropoietin (EPO) secretion is suppressed, creating suspicion that the process is initiated by a fall in EPO levels below a threshold. On descent from altitude, low doses of subcutaneous EPO prevented a rapid adaptive fall in red cell mass, further implicating low EPO levels in precipitating this process.[4]

Renal insufficiency presents a pathologic situation in which EPO is depressed. We sought to determine whether neocytolysis is present in some patients with renal insufficiency and contributes to their anemia. If so, important implications might extend to optimizing therapy for the anemia of renal disease.

Methods.

From among 9 stable dialysis patients screened, five were selected for study and gave informed consent. Patients were selected on the basis of no active infection or inflammatory diseases, no iron deficiency based on serum ferritin levels, and low baseline EPO levels (all less than 25 units/ml) (Ramco, Houston). These patients were studied during regular EPO therapy (generally 50 μ/kg/tiw SQ) and for at least 12 days while EPO was held.

All patients had red cell labeled with 50 μCi ^{51}Cr and survival curves traced by standard methods both on and off EPO.[5] Three patients were administered 1 gm oral ^{13}C-glycine and ^{15}N-glycine, one isotope during standard EPO therapy and one prior to holding exogenous EPO. Serial stool specimens were collected and stercobilin was isolated by ethanol, ether and chloroform extraction,[6] and a final thin layer chromatography step.[7] Specimens were frozen at -20°C until analyzed for ^{13}C and ^{15}N by mass spectroscopy.[8]

Results

The figure shows a typical patient ^{51}Cr-red cell survival curve, with the slope steeper during the first 9 days (off EPO) than after 9 days (EPO therapy resumed). For all five patients, the survival curve slope for the first 9 days off EPO was - 2.24 days (SD 0.34) and the subsequent slope was -1.12 days (SDO. 47). Survival is statistically shorter in the first 9 days off EPO ($p < .05$).

In the 3 patients who received oral ^{13}C-glycine and ^{15} N-glycine, two had abnormal enrichment of their stool with the isotope administered just before EPO was held. The third patient showed abnormal stool enrichment by both isotopes. This patient also had the shortest ^{51}Cr-red cell survival and appears to have a chronic hemolytic process.

Discussion

Neocytolysis has been observed with physiologic EPO suppression in astronauts and in polycythemic individuals descending from high altitude, and it has been prevented by administration of low doses of EPO.[1-4] This mandated the study of a situation in which there is pathologic EPO suppression, the anemia of renal insufficiency. When five dialysis patients with low baseline EPO had their EPO therapy withheld, a pattern of neocytolysis emerged in four (the fifth showing a pattern of chronic hemolytic anemia). ^{51}Cr-red cell survival curves showed a statistically steeper slope in the first nine days after EPO was held, a pattern consistent with neocytolysis.

Stool porphyrins were studied in two of the four patients with a pattern of neocytolysis and both showed selective abnormal stool enrichment of the isotope administered at a time that only young red cells (neocytes) would be labeled. This confirms selective hemolysis of young red cells when EPO is withheld.

The anemia of renal disease was long regarded multifactorial in most patients, but the extraordinary clinical efficacy of recombinant erythropoietin clearly establishes erythropoietin deficiency as paramount.[9] Too quickly disregarded are studies demonstrating a consistent hemolytic component of variable degree in the anemia of renal insufficiency,[10-12] an extracorpuscular hemolytic component never fully explained.[13] Neocytolysis can explain this hemolytic component without negating the therapeutic efficacy of erythropoietin; after all, prevention of neocytolysis appears as a newly-recognized action of erythropoietin.[4] Further support for this concept comes from Eschbach's observation that erythropoietin therapy prolongs red cell survival in renal diseases.[14]

Neocytolysis predicts inefficiency of intravenous bolus dosing schedules of recombinant erythropoietin. The erythropoietin peak would effect commitment and proliferation of erythroid progenitors, but the nadir would bring neocytolysis of newly-released red cells. Neocytolysis might better explain the metabolic toxicities of hyperkalemia and hyperphosphatemia that have been observed with bolus erythropoietin therapy.[9] Quite a number of empiric studies have shown that subcutaneous erythropoietin injections are more effective then intravenous boluses at considerably lower total doses and cost.[15,16] Investigators have been unable to satisfactorily explain the basis of this phenomenon, but avoidance of nadirs which precipitate neocytolysis explain it nicely.

In summary, neocytolysis is a physiologic process allowing rapid adaptation to plethora by selectively hemolyzing young red blood cells, apparently precipitated by EPO depression. We now demonstrate its occurrence in four of five studied dialysis patients. In the anemia of renal disease, neocytolysis helps to explain the (1) often demonstrable hemolytic component, (2) worse hemolysis with more advanced renal disease,[11] (3) responsiveness of hemolysis to erythropoietin therapy, (4) metabolic side-effects of intravenous bolus erythropoietin, and (5) increased efficiency of daily subcutaneous erythropoietin. Having shown that neocytolysis can contribute to anemia in renal failure patients with low EPO baselines and not on active therapy, we are launching studies of the intensity of neocytolysis in patients on intravenous bolus versus low-dose daily subcutaneous erythropoietin therapy.

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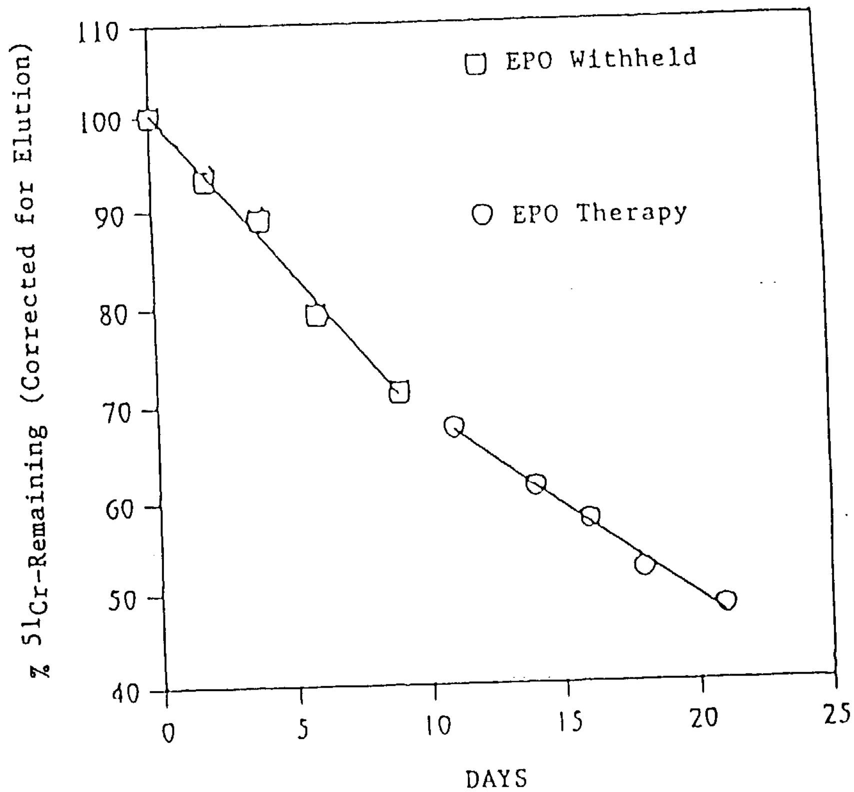

Figure. 51Cr-red cell survival curve of patient 1 when EPO therapy is withheld. The slope during the first 9 days (-3.24) is steeper than after 9 days (-2.00).