Effect of Erythrocyte Mass on Arterial Blood Pressure in Dialysis Patients Receiving Maintenance Erythropoietin Therapy

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Abstract

Treatment of renal anemia with recombinant human erythropoietin (rEPO) frequently raises arterial blood pressure. The objective of this study was to determine whether this is a direct effect of rEPO or a consequence of the expansion of erythrocyte mass. Twenty-three chronic hemodialysis patients receiving maintenance rEPO therapy who had uncontrolled anemia due to iron deficiency were studied. It was anticipated that repletion of iron stores with iv iron dextran would restore rEPO responsiveness, leading to a gradual rise in hematocrit to the target values (0.30 to 0.33). The effect of the increase in hematocrit on arterial blood pressure could then be dissected from the direct effect of rEPO in patients receiving constant doses of rEPO throughout the study period. To this end, arterial blood pressure, iron indices, hematocrit, and measures of fluid balance were monitored at baseline and for a 10-wk period after iron repletion. In eight patients, the hematocrit transiently rose above 0.33, triggering a reduction in rEPO dosage. In the remaining 15 patients, rEPO dosage was held constant during the study period. In this subgroup, repletion of iron stores led to a rise in hematocrit from 0.25 ± 0.04 to 0.32 ± 0.04 (P < 0.001) within 4 wk. Despite the significant rise in hematocrit, both systolic and diastolic blood pressure values remained virtually unchanged. Likewise, body weight and interdialytic fluid gain were unaltered. Furthermore, no patient required alteration in the type or dosage of antihypertensive medications during the observation period. In conclusion, a slow rise in hematocrit to the range of 0.30 to 0.33 in hemodialysis patients treated with constant doses of rEPO has no effect on arterial blood pressure. Thus, the effect of rEPO on arterial blood pressure does not appear to be related to the associated rise in erythrocyte mass within the limits of the hematocrit values reached in this study.

Key Words: Erythropoietin, anemia, hypertension, iron dextran
rameters during a period when rEPO was administered regularly without adequate control of anemia. We continued to monitor these parameters for a period of 10 wk after iv administration of the new iron dextran preparation, which restored rEPO responsiveness and anemia control. As expected, a significant increase in hematocrit occurred in most cases, whereas rEPO dosages remained unchanged. Accordingly, this unusual situation allowed us to dissect the effect of a gradual increase in hematocrit on arterial blood pressure from the direct effect of rEPO, the dose of which was constant throughout the observation period.

PATIENTS AND METHODS

Twenty-three patients with ESRD maintained on hemodialysis participated in the study. They included all of the patients receiving maintenance dialysis in our facility who were iron deficient, as judged by a serum ferritin concentration below 100 ng/mL and/or transferrin saturation below 20%, and who had received rEPO (Epogen®; Amgen, Inc., Thousand Oaks, CA) iv with each dialysis treatment for at least 3 months before the study. Patients were excluded if there was evidence of acute or chronic infection, congestive heart failure, acute intercurrent illness, or adverse reaction to an iv test dose of iron dextran.

There were 14 men and 9 women, aged 52 ± 12 yr (range, 25 to 72 yr). Duration of dialysis before the study was 4.7 yr (range, 1 to 9 yr). Causes of ESRD included diabetic nephropathy (N = 6), ESRD of unknown etiology (N = 6), chronic glomerulonephritis (N = 4), chronic pyelonephritis (N = 2), and the following conditions in one case each: hypertensive nephrosclerosis, polycystic kidney disease, obstructive uropathy, chronic interstitial nephritis, and membranoproliferative glomerulonephritis. Seventeen patients were receiving antihypertensive medications.

All patients received hemodialysis thrice weekly for 3 hours with hollow fiber dialyzers made of polyacrylonitrile (AN69; Hospal, Lyon, France) or cellulose acetate membranes (Baxter, Round Lake, IL), a bicarbonate-buffered dialysate, and single-pass volumetric-controlled dialysate delivery systems (Baxter 550, Round Lake, IL). Calcium carbonate or aluminum carbonate was used as a phosphate binder, and multivitamin preparations and folate were used to prevent deficiency states. Antihypertensive agents were used when needed to control hypertension. Sodium, potassium, and fluid restrictions were prescribed to avoid hyperkalemia and volume overload, respectively. Oral iron supplements were continued throughout the study. Patients whose hematocrit rose above 0.33 during the study period had their rEPO dosage reduced or temporarily withheld.

For each patient, the systolic and diastolic blood pressures, body weight, interdialytic weight change, hematocrit, dosages of rEPO, and other medications were recorded for the week before the first dose of iv iron and then thrice weekly during the ensuing 10 wk. The means of the values recorded for each parameter during the week preceding the first dose of iv iron were used as the baseline values. Blood pressure was measured with mercury manometers immediately before each dialysis session, after 5 min of quiet sitting, by the technique recommended by the American Heart Association.

After a test dose of 5 mg, iron dextran (InFeD®; Schein Laboratories, Phoenix, AZ), 100 mg, was administered iv during each of 10 consecutive dialysis treatments. None of the patients exhibited a hypersensitivity reaction to this preparation.

Complete blood count, serum iron, total iron-binding capacity (TIBC), and ferritin concentrations were determined by routine laboratory methods. Percent transferrin saturation was calculated with serum iron and TIBC values.

Data Presentation and Statistical Analysis

Data are presented as mean ± SD unless otherwise noted. Day 0 was considered to be the day when the first dose of iv iron dextran was administered. Multiple measure analysis of variance and paired and unpaired t tests were used as appropriate. P values < 0.05 were considered significant.

RESULTS

Hematopoietic Effects

In eight patients, the dose of rEPO was reduced during the study period because of the rise of hematocrit above 0.33. Blood pressure data for this subgroup were analyzed separately from the remainder of the group.

In the 15 patients in whom the rEPO dosage was held constant during the study period, hematocrit increased from 0.25 ± 0.04 at baseline to 0.32 ± 0.04 at Day 25 (P < 0.01) (Figure 1). All subjects exhibited a rise in hematocrit, whereas 13 of the 15 patients achieved a hematocrit within the target range of 0.30 to 0.33, as set by the U.S. Department of Health and Human Services (HHS). In most cases, the target hematocrit was reached within 1 month after the initiation of parenteral iron administration. The rEPO dose in this group was 3,800 ± 2,660 IU thrice weekly (range, 1,000 to 8,000 IU) and was unchanged during the study period (Figure 1).

Effect on Blood Pressure and Fluid Balance

As can be seen in Figure 1, systolic and diastolic blood pressures remained virtually unchanged dur-
DISCUSSION

The pathophysiology of hypertension in ESRD patients receiving rEPO has been the subject of considerable study and speculation, and it now appears likely that several factors are involved in the development or aggravation of hypertension in this setting.

Typically, ESRD patients with uncontrolled anemia exhibit a hyperdynamic circulation, with tachycardia and elevated cardiac output. Peripheral vascular resistance in this population is usually normal, despite the presence of several factors that tend to lower the systemic vascular resistance, e.g., low blood viscosity, hypoxic vasodilation, and the presence of low-resistance arteriovenous shunts used for hemodialysis access (14). Partial correction of renal anemia by rEPO administration is often associated with reductions in heart rate and cardiac output (14), which tend to offset the effects of the associated increase in vascular resistance. Nonetheless, an apparent mismatch between the rise in vascular resistance and the fall in cardiac output leads to a net rise in arterial pressure in many rEPO-treated patients.

Effect on Iron Indices

With iron dextran administration, TIBC decreased (240 ± 57 versus 205 ± 56 µg/dL; P < 0.01), whereas ferritin concentration and transferrin saturation increased significantly (82 ± 57 versus 239 ± 131 ng/mL; P < 0.001; and 15 ± 6 versus 23.3 ± 13.6%; P < 0.01, respectively). However, the rise in serum iron concentration did not reach statistical significance (35.4 ± 17 µg/dL versus 48.0 ± 35.2 µg/dL; P = not significant).
patients with ESRD. Although consensus exists as to the role of increased vascular resistance in the pathogenesis of rEPO-associated hypertension, the question remains on the relative role of a hematocrit-mediated, as opposed to a possible direct or indirect vasoconstrictive, effect of rEPO. This study was intended to address this issue.

The patients included in this study were receiving rEPO for a period of at least 3 months, during which they had uncontrolled anemia due to iron deficiency. Accordingly, the effect, if any, of rEPO on blood pressure during this period was unrelated to its erythropoietic action, i.e., erythrocyte mass or hematocrit. With the subsequent repletion of iron stores, erythropoietic response was restored and hematocrit rose to or, in eight cases, transiently exceeded the range of target values (0.30 to 0.33) established by the U.S. Department of Health and Human Services. Given the constancy of the antihypertensive medications and fluid balance in the subgroup (N = 15) in whom rEPO dose remained constant during the study period, any change in arterial blood pressure could have been reasonably attributed to either restoration of iron stores or the rise in hematocrit. However, arterial blood pressure remained virtually unchanged, despite a marked and relatively rapid rise in hematocrit. This observation strongly suggests that the rise in hematocrit within the limits observed in this study had no discernible effect on arterial blood pressure. Accordingly, the possible contribution of rEPO to the arterial pressure in the study population must be unrelated to the resultant rise in hematocrit and erythrocyte mass. It should be noted, however, that, in compliance with the HHS guidelines, we kept the hematocrit values close to the recommended range of target values. Therefore, these conclusions may not be extended to circumstances where hematocrit is allowed to rise above 0.33.

As to a possible effect of iron, per se, lack of any change in blood pressure during the period when iron dextran administration was initiated and before a rise in hematocrit was observed rules against such a possibility.

The independence of the rEPO-induced rise in blood pressure from its effect on erythrocyte mass shown in this study is consistent with a number of earlier observations (11,12). For example, Baskin and Lasker reported a rise in blood pressure preceding the rise in hematocrit in five patients treated with rEPO (11). In another study, Pascual et al. noted a need for increased antihypertensive medications in a small group of patients within the first month after rEPO therapy, despite minimal increments in hematocrit (12). The dissociation between erythrocyte mass and rEPO-induced hypertension is clearly illustrated by recent studies reported by Vaziri et al. in animals with experimental renal insufficiency (16). This is further supported by a single case report of severe hypertension occurring with the correction of anemia with rEPO, but not with blood transfusion yielding an identical hematocrit (17).

Several studies have suggested that rEPO may exert a direct vasoconstrictive effect by which it elevates blood pressure. Heidenreich et al. have demonstrated a dose-dependent, endothelium-independent vasoconstrictive effect of rEPO in isolated murine renal and mesenteric resistance vessels in vitro (9). The mechanism of the vasoconstrictor effect, if any, of rEPO is uncertain. rEPO does not appear to significantly increase plasma catecholamines, renin, or angiotensin II levels (18,19). However, Carlini et al. (10) found that raising hematocrit to 0.31 to 0.33 with rEPO increased plasma endothelin levels, which in turn correlated strongly with the magnitude of rise in mean arterial pressure. They further showed that patients treated with sc rEPO for the same period achieved similar hematocrit values with half the amount of rEPO without experiencing a rise in either blood pressure or plasma endothelin level (10).

Most forms of primary and acquired hypertension are characterized by elevated cytosolic ionized calcium concentration ([Ca2+]i). It is, therefore, of interest that rEPO raises platelet [Ca2+]i. In ESRD patients and in spontaneously hypertensive rats, but not in their normotensive counterparts (Wistar-Kyoto) (20). In this regard, a genetic predisposition to rEPO-associated hypertension, i.e., positive family history, has been suggested in ESRD patients (21). The extent to which altered cytosolic cation homeostasis, whether genetically determined or acquired, influences the occurrence of rEPO-induced hypertension is unclear and requires further investigation.

In conclusion, we have clearly shown that a rise in hematocrit to 0.30 to 0.33 in ESRD patients treated with constant doses of rEPO has no effect on arterial blood pressure. This observation proves that an rEPO-associated rise in blood pressure is not due to the rise in hematocrit.

REFERENCES

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