Angiotensin converting enzyme inhibitors impair recombinant human erythropoietin induced erythropoiesis in patients with chronic renal failure

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ABSTRACT

Objectives: To investigate the effects of angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and other anti-hypertensive agents on recombinant human erythropoietin (rHuEPO) in chronic renal failure (CRF) patients.

Methods: The present study was conducted at the Nephrology Department, Khan Research Laboratories Hospital and Quaid-i-Azam University, Islamabad, Pakistan during March 2004 to February 2005. One hundred patients, 55 males and 45 females (age range 13-78 years) were divided into 2 groups. Group-I patients received rHuEPO and ACE inhibitors/ARBs while Group-II patients received rHuEPO with other antihypertensives such as calcium channel blockers or β-adrenergic receptor blockers. Monthly increment in hematocrit (HCT%) was monitored in both groups for 4 continuous months. One-way ANOVA on Dunn's, univariate and multivariate analyses were carried out to determine any significant improvement in erythropoiesis between the 2 treatment groups.

Results: Monthly increase in HCT% was significantly greater in the group that was treated with rHuEPO and antihypertensives other than ACE inhibitors/ARBs compared with that treated with ACE inhibitors/ARBs, an effect observed even at a higher dose of rHuEPO, and the patients were iron replete.

Conclusion: The present data from our population confirms that ACE inhibitors/ARBs interfere with rHuEPO therapy for treatment of anemia in CRF. The ACE inhibitors/ARBs inhibit erythropoiesis induced by rHuEPO in CRF patients, therefore, simultaneous use of ACE inhibitors/ARBs and rHuEPO should be carried out with caution.

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Anemia and hypertension are frequent occurrences in patients with chronic renal failure (CRF) and contribute significantly to morbidity and mortality. Anemia mainly results due to lack of endogenous erythropoietin (EPO) production from failing kidneys. To counter anemia, patients with CRF are regularly treated with erythropoietin, iron and other hematenics.[1] Cardiac enlargement, left ventricular hypertrophy, congestive heart failure, and angina are the complications particularly associated with anemia.[2] Hypertension however, is commonly treated with antihypertensive agents; angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Drugs such as enalapril (ACE inhibitor) and losartan (ARB) are reno-protective in action as they cause a reduction in blood pressure, urinary albumin excretion and histological damage.[3] Despite protective antihypertensive actions, ACE inhibitors are known to reduce EPO levels or induce resistance to EPO in CRF patients treated with recombinant human erythropoietin (rHuEPO).[4] It has also been shown that ACE inhibitors/ARBs inhibit response to EPO, particularly at high doses.[5] Additionally, ARBs can directly inhibit erythropoiesis in vitro.[6] Enalapril is known to cause reduction of hematocrit (HCT) in both hypertensive patients and healthy volunteers.[7] Moreover, ACE inhibitors decrease hematocrit in patients with post-renal transplant erythrocytosis, although by mechanisms other than changes in the circulating EPO.[8] Similarly, losartan decreases hematocrit in patients with post-transplant erythrocytosis.[9] There does not appear to be a unifying mechanism of action by which ACE inhibitors/ARBs exert their effect on erythropoiesis. Possible mechanisms include a direct decrease in circulating ACE levels or interference of binding with angiotensin 1 (AT1)

receptors leading to a loss of stimulatory effect of ACE on erythroid progenitor cells[10] as well as increased plasma levels of N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) by generating its degradation. Increased plasma Ac-SDKP in turn prevents the cycling of hematopoietic stem and progenitor cells.[11] Renin angiotensin system (RAS) is linked to the production of endogenous EPO from the peritubular fibroblasts of kidney.[12] The ACE is central to RAS and converts AT1 to angiotensin II.[13] Furthermore, increased renin expression has been detected in afferent arterioles in animals with CRF. Augmentation of intra-renal angiotensinogen, an enzyme homologous to renin, was also reported in experimental hypertension induced by angiotensin II infusion.[14] Experiments with ACE inhibitors or AT1 receptor antagonists have suggested that the effects of angiotensin II on the kidneys can be local, through its receptors on renal cells or systemic via its hypertensive actions.[15] Pharmacological blockade of angiotensin II attenuates glomerular damage independent of blood pressure in most disease conditions including diabetic nephropathy,[16] but suppression of angiotensin II production may inhibit EPO synthesis, reducing its circulating levels and thus exacerbating anemia.[17] Several studies have been conducted worldwide on the effects of ACE inhibitors/ARBs on rHuEPO induced erythropoiesis in CRF patients but the reports are contradictory. Moreover, no such report exists on Pakistani patients to find a place in existing data from different world populations. The present investigation was therefore aimed at investigating the effects of ACE inhibitors/ARBs interfering with erythropoiesis and to compare if anti-hypertensive agents other than these behave similarly during therapy with rHuEPO in CRF patients.

Methods. The study was approved by the Ethics Committee for Research on Human Subjects, Pakistan Medical Research Council, Ministry of Health, Islamabad and written informed consent was obtained from each subject after explaining to each one of them the study procedures. One hundred and fifteen CRF patients (age range: 13-78 years) from the cities of Islamabad and Rawalpindi were considered for the study. All these patients were on hemodialysis and were iron replete. They were divided into 2 groups. Group-I (n=55) received rHuEPO and ACE inhibitors (captopril, enalapril, lisinopril, and so forth) or ARBs (valsartan). One patient died during the study, one was lost to follow up, 3 were non-compliant, and 2 underwent renal transplant. Of the remaining 48 patients, 26 (54.2%) were males (age range 16-72 years; body weight 42-85 kg), and 22 (45.8%) were females (age range 22-69 years; body weight 48-66 kg). Group-II (60 patients) received rHuEPO with antihypertensive drugs other than ACE inhibitors such as β-blockers (atenolol, metoprolol, and so forth), and calcium channel blockers (nifedipine, amlodipine, and so forth). In this group, 3 patients died, 3 were lost to follow up, one had renal transplant, and one was non-compliant; of the remaining 52 patients, 29 (55.8%) were males (age range 15-78 years; body weight 39.5-84 kg), and 23 (44.2%) were females (age range 13-70 years; body weight 35-79 kg). Patients were also grouped on the basis of baseline hematocrit, history of dialysis, dose of rHuEPO, any underlying disease and use of any iron preparation. The change in hematocrit was compared between the 2 groups on a monthly basis consecutively for 4 months. Iron deficient patients were supplemented orally with iron (Tablet Trihemic-H or Capsule Fefol-Vit, FK & F Co.) once daily or parenteral iron therapy as intravenous Venofer, (Vifor Co.) injections at the dose of 1 g/L normal saline. Inclusion criteria were CRF patients under treatment with rHuEPO and anti-hypertensive agents. Exclusion criteria were non-compliance with dialysis schedule or treatment; patients having EPO resistance as evidenced by the iron deficiency not controlled with oral or parenteral iron or unable to take iron preparation due to side effects; severe chronic inflammation; severe hyperthyroidism; received blood transfusion during the study period or underwent renal transplantation. Patients were given rHuEPO subcutaneously as formulation of Eprex (Janssen-Cilag) in dosage range of 51-114 U/kg body weight twice or thrice at the time of each dialysis, depending upon the condition of patients, whether they needed dialysis twice or thrice a week. The ACE inhibitors/ARBs were given in the following doses: captopril 25-75 mg/day; enalapril maleate 2.5-2.0 mg/day; lisinopril 5-20 mg/day; losartan 50 mg/day; valsartan 160 mg/day. During the 4-month study period, blood complete picture was carried out on an automated hematology analyzer Sysmax (KX-21) and HCT% values thus obtained were analyzed. The HCT values of both groups obtained monthly were compared by Dunn's method using one-way ANOVA. Change in HCT values between the 2 groups was compared using multiple regression analysis. Univariate analysis was applied to compare mean HCT of both groups. Application of multivariate analysis further revealed the effects of different variables on change in HCT in both groups. Probability $p<0.05$ was considered a statistically significant difference using the Statistical Package for Social Sciences version 10.

Results. The patients' histories demonstrated that in Group I, 17 males and 13 females had <1 year history of dialysis while 9 males and 9 females presented a dialysis history of >1 year. In Group II, CRF patients comprised

23 males and 17 females with dialysis history of <1 year whereas 6 males and 6 females showed dialysis history of >1 year. The baseline HCT of Group I in the first month was 24.80 ± 8.81% that increased to 26.95 ± 9.17% over the first, 28.85 ± 9.50% over the second, 30.95 ± 9.90% over the third and 32.95 ± 10.32% over the fourth month. In Group-II, baseline HCT was 24.55 ± 5.82% that increased to 27 ± 5.64% over the first, 29.65 ± 5.49% over the second, 32.30 ± 5.38% over the third, and 35 ± 5.28% over the fourth month. The difference of HCT between the 2 groups was significant (p<0.001) showing an increase of HCT in Group II. The increase in HCT in Group I was 2% while in Group II it was 2.4% even though Group I patients were dosed with 54.8 - 117.64 U/Kg while the dosage for Group-II patients was 51.28 - 114.2 U/kg rHuEPO (**Table 1**). Multivariate analysis was applied keeping HCT as a dependent variable while age, gender, weight, group, dose of rHuEPO, underlying disease in Group I and Group II as constant variables. A significant difference (p<0.05) was obtained between the HCT values of the 2 groups while no other variable showed any association with HCT (**Table 2**).

Table 1 - Monthly increase in HCT% and dose of rHuEPO of the 2 groups. Values are presented as mean ± SD.

Parameters	Group I N = 48	Group II N = 52
Monthly increase in HCT%	2.09 ± 0.20	*2.41 ± 0.15
	range 1.45-2.50	range 2.07-2.75
rHuEPO dose (U/kg)	72.64 ± 13.10	69.64 ± 40.81
	range 54.80-117.64	range 51.28-114.2

* Shows significant difference p<0.001,
HCT - hematocrit, rHuEPO - recombinant human erythropoietin

Table 2 - Multivariate analysis between Group-I and Group-II keeping hematocrit as a dependent variable.

Variables	t-value	*P*-value
Age	0.05	0.96
Gender	-0.99	0.324
Weight (kg)	0.48	0.634
History of dialysis	-0.46	0.648
rHuEPO dose	0.28	0.781
Groups		
I - rHuEPO+ACE inhibitors/ARB II - rHuEPO+other	7.53	0.000*
Antihypertensives		
Underlying disease Group-I	0.98	0.320
Underlying disease Group-II	-0.04	0.966

* Shows significant difference p<0.000, ARB - angiotensin receptor blocker, rHuEPO - recombinant human erythropoietin

Discussion. Angiotensin converting enzyme inhibitors and ARBs that are routinely prescribed to CRF patients for the treatment of hypertension, left ventricular dysfunction and diabetic nephropathy are known to interfere with the process of erythropoiesis initiated by rHuEPO.[18] The first report of an interaction between ACE inhibitors and EPO was presented by Walter.[19] Since then several studies have been conducted worldwide to examine the relationship between concomitant use of rHuEPO and ACE inhibitors to treat anemia and hypertension but the results are conflicting. The focus of the present study was to compare the effect of ACE inhibitors/ARBs and other anti-hypertensive agents on erythropoietin therapy in CRF patients. Currently, the HCT rise was 2% with rHuEPO in patients taking ACE inhibitors/ARBs, which was significantly lower than those receiving antihypertensive drugs other than ACE inhibitors/ARBs. A previous study provides evidence that a high dose of rHuEPO is required to treat anemia in patients taking an ACE inhibitor enalapril.[20] Although, there occurred a linear increase in monthly HCT in both treatment groups, this elevation was significantly greater in patients being treated with antihypertensive drugs other than ACE inhibitors and it is also noteworthy that even a higher dose of rHuEPO remained unable to increase HCT. Hayashi et al',[21] however, found no difference between patients with and without ACE inhibitors therapy when hemoglobin and rHuEPO dose requirements were compared. The present study in contrast shows that concomitant use of ACE inhibitors and rHuEPO does affect erythropoiesis, and that the combination therapy should be given with caution and only when utmost necessary. Our results in Pakistani CRF patients further confirm Macdougall et al's,[22] observations on the effect of ACE inhibitors/ARBs on erythropoietin therapy in CRF patients from Japan.

Treatment of CRF anemia with rHuEPO accelerates erythropoiesis but induces functional iron deficiency due to increased iron requirement resulting in EPO resistance. Therefore, intravenous iron supplementation becomes necessary to improve response to EPO treatment.[10] It should be noted that all the patients considered for the present study were iron replete and therefore less increase in HCT observed in Group I was quite possibly due to interference of ACE inhibitors/ ARBs with rHuEPO and apparently not due to any iron deficiency. It was demonstrated earlier that the use of rHuEPO at a low dose, and ACE inhibitors at a high dose inhibit erythropoiesis. In the United States and Europe the starting dose of rHuEPO is 50-100 U/kg body weight 3 times/week while in Japan 3000 U of rHuEPO is given thrice a week until HCT reaches 30% and afterward the dose is reduced to 1500 U twice a

week. Similar variations in the dosage regimen of ACE inhibitors is observed globally. The ACE inhibitors like, enalapril are recommended in Pakistan at the dose range of 2.5-20 mg/day and captopril as 25-75 mg/day. However in other countries like United States and Europe; 10-40 mg/kg enalapril, and 450 mg/kg captopril are given whereas in Japan; enalapril and captopril are used at dose ranges of 5-10 mg/day and 37.5-75 mg/day, similar to those used currently. Thus, the dose range for ACE inhibitors/ARBs used presently was on the lower side, and rHuEPO was on the moderate side (55-114 U/kg body weight).

The ACE inhibitors/ARBs are known to cause hyperkalemia which may influence erythropoiesis induced by exogenous rHuEPO.[23] Consequently, a higher dose of rHuEPO is required, it is suggested therefore that it should be reserved for dialysis patients with hypertension uncontrolled with other antihypertensive medications or dialysis patients with cardiac failure.[4] It is accepted that the present study was conducted on a small number of patients, which warrants further studies to be conducted at a larger scale with a greater number of patients taken from throughout the country to get more meaningful data on CRF patients under these conditions. Nonetheless, our study concludes that Pakistani CRF patients receiving rHuEPO for anemia treatment and ACE inhibitors/ARBs for hypertension face similar impairment of erythropoiesis as has been observed worldwide. Consequently, it is suggested that during therapy with rHuEPO, ACE inhibitors/ARBs should be given to CRF patients with prudence and at a low dose if no alternative is available. The current outcome raises the need to identify and characterize antihypertensive agents non-interfering with rHuEPO during anemia treatment in CRF patients.

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