Original Article

Assessment of Enalapril Effect on Inducing Anemia In Non-Azotemic Diabetic Patients

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ABSTRACT

Background: Angiotensin converting enzyme inhibitors (ACEIs) are known to induce anemia following renal transplantation, dialysis and in renal failure patients. It seems that ACEIs cause anemia via inhibition of erythropoietin synthesis or inhibiting normal proliferation of early erythroid progenitors, which are normally stimulated by angiotensin converting enzyme. There are few reports on how ACEIs induce anemia in non-azotemic diabetic patients. We studied the effect of enalapril on inducing anemia in non-azotemic diabetic patients.

Methods: This study included 94 diabetic non-azotemic patients (serum creatinine (sCr) ≤1.5 mg/dl by jaffe reaction). Patients were divided into two groups, the first; with clinical proteinuria (P+) having a 24 hour urine protein ≥300 mg or positive urine dipstick for protein, at least on two of three times tested, with an interval of 1 month and the second group without any signs of clinical proteinuria (P-). Only 32 patients completed the course of study; 17 as P+ and 15 as P-. Patients in both groups received 10 mg enalapril daily; and every 3 months, the dose was doubled until the dose of 40 mg/day was reached, unless any side effects emerged. Hemoglobin concentration (Hb), sCr and serum potassium (K^+) were also checked regularly. Data were analyzed using t-Student test, paired t test, and chi-square test. A p value < 0.05 was considered as significant.

Results: Both groups of patients were matched from the standpoint of age and sex. The average baseline sCr in P+ and P- groups were 0.8 ± 0.19 mg/dl and 0.8 ± 0.18 mg/dl respectively.(p = 0.97)

After the study was completed, the average baseline sCr rose to 0.99±0.19 and 0.92±0.22 mg/dl in P+ and P- groups respectively. (p=0.32)

In P+ group, mean Hb was 14.1 ±1.30 g/dl and 13.9 ± 0.99g/dl before and after the study respectively.(p = 0.28)

The same parameter for the P- group was measured as 14.1±1.00 and 12.9±3.30 before and after the study respectively.(p=0.16)

Conclusion: This study shows that enalapril has no significant effect on inducing anemia in non-azotemic diabetic patients.

Key Words: Enalapril, Anemia, Diabetes, Proteinuria

Angiotensin Converting Enzyme Inhibitors (ACEIs) are known to cause anemia in patients on dialysis, in chronic renal failure[1, 2] and following renal transplantation[3,4,5]. In addition, patients who develop erythrocytosis after renal transplantation, are commonly treated with ACEIs[6]. Since angiotensin II is proved to be necessary for production of erythropoietin in animals and also in humans[5],therefore inhibition of angiotensin II inhibits erythropoietin synthesis and RBC production[6]. Anemia in such patients is suggested to be due to a decrease in red blood cell (RBC) production, however the precise mechanism of anemia is still unknown[6].

The direct effect of angiotensin II on proliferation of RBC progenitor cells was shown by Murg et al in 1997 [7]. ACEIs including enalapril and captopril are the drugs of choice in the treatment of hypertension in diabetics. These drugs are recommended for treatment of proteinuria in diabetic patients with or without hypertension as well. ACEIs are proved to reduce blood pressure, proteinuria and progression of renal failure in diabetic patients as

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compared to control groups[8]. As far as we know, there have been few studies on the role of ACEIs in inducing anemia in non- azotemic diabetic patients.

The purpose of this study was to find whether enalapril could induce anemia in non-azotemic dia betics, and if there were any relationship between the dose of enalapril and development of anemia.

Materials and Methods

The study was carried out in the Endocrine and Metabolism Research Center (EMRC), Amin hospital, Isfahan, Iran, from 1999 to 2003.

All referred diabetic patients who had a serum creatinine level < 1.5 mg/dl and had not received ACEIs for at least the last 2 months were chosen, provided that they met the inclusion criteria.

Inclusion Criteria

1- Normal renal function (serum creatinine < 1.5 mg/dl by jaffe colorimetric method) [9,10]
2- Normal Hb concentration (Hb > 11.7 g/dl in women and > 13.2 g/dl in men) [11] and transferrin saturation [serum Iron(Fe) / Total Iron Binding Capacity(TIBC)] > 15%
3- Presence of diabetes mellitus (fasting blood sugar > 126 mg/dl)
4- No previous use of ACEIs for at least 2 months (A period of two months is enough for the wash out of the probable effect of ACEIs on inducing anemia)
5- Absence of pregnancy
6- Absence of malnutrition, hypothyroidism, malignancy, pulmonary, cardiac, hepatic and hematopoietic disease and recent bleeding

These conditions were ruled out with a careful history taking, physical examination and if necessary applying lab testing.
7- No recent use of theophylline, azathioprine and cyclophosphamide (due to the possibility of developing anemia)

Exclusion Criteria

1- Azotemia
2- Developing clinical proteinuria in the group without proteinuria
3- Pregnancy
4- Low compliance
5- Drug side effects (Systolic blood pressure < 100 mmHg, Cough, Hyperkalemia (K^+> 5 mEq/L) and Agranulocytosis).

A General physician or an internist first evaluated the diabetic patients who referred to EMRC. If they met the inclusion criteria, they were selected and then necessary lab tests were requested and were followed by a nephrologist.

The nephrologist did not change the patients' medications except antihypertensive drugs if the patient developed low blood pressure. The same nephrologist visited every patient monthly.

A sample size of 15 for each group was calculated as statistically reliable.

We applied convenience sampling method for choosing the case and control patients. All patients were fully informed of the study and each signed the letter of consent. Then they were tested for Hb, Hct (Hematocrite), BUN (Blood Urea Nitrogen), sCr, Fe, TIBC, Potassium (K^+), and urine protein. Patients were assigned as anemic when they had a Hb ≤ 11.7 g/dl in women and ≤ 13.2 g/dl in men, or a decrease in Hb concentration≥ 10% from their baseline Hb concentration.[11] Patients were divided into two groups according to the presence or absence of clinical proteinuria (having a 24 hour urine protein ≥300 mg or positive urine dipstick for protein, at least on two of three occasions tested, with an interval of 1 month).

Enalapril Maleate tablet (Dr. Abidi Pharmaceutical Co, Tehran, Iran), 10 mg/day was prescribed for 3 months and every 3 months the dose was doubled until 40 mg/day.

Two weeks after beginning or changing the dose, serum Cr and K^+ were measured. Hb was also measured every 45 days.

In case of developing anemia, serum iron, TIBC, ferritin, guaiac test, reticulocyte count, and LDH (Lactic Dehydrogenase) were assessed to rule out other causes of anemia.

Enalapril was taken for 9 months and in case anemia emerged, the drug was discontinued and Hb was checked again every 45 days to evaluate rising of Hb.

Results were expressed as mean ± SD. Comparisons between the two groups before and after the study were made by paired t-test and t student-test. Comparisons between the two groups for nominal variables were made by Pearson chi-square test.

SPSS software version 11.5 was used for analysis on a computer.
A p value < 0.05 was considered as statistically significant.

Results

During a 4-year study, 244 patients were evaluated. A hundred and ninety five patients who were non-azotemic and did not use enalapril for at least the previous 2 months were selected, and then were tested for Hb, Hct, Fe, and TIBC as primary lab exams. From 195 patients, 101 patients were excluded for failing to do the lab tests or having an abnormality in the test results. From the patients included in this study, 7.4% or 7/94 patients (6 F and 1 M) due to anemia (iron deficiency) and blood transfusion, 14.8% or 14/94 (3 M and 11 F) due to development of cough, 6.3% or 6/94 (5 F and 1 M) due to hyperkalemia, and 6.3% or 6/94 due to azotemia during the study, (totally 33) were excluded. Another 29 patients did not follow the study, mainly because of personal reasons.

Sex distribution of the two groups is presented in table 1.
The range of age varied from 20 to 72 years in P+ group and from 40 to 68 years in P– group.
The mean age in the P+ and P- group was 51.6 ±13 and 55.9 ± 08 years respectively. (p = 0.28)
The Δ Hb (before and after the study) in P+ and P- groups were 0.23 ± 0.83 and 1.18 ± 3.1 g/dl respectively. (p = 0.2)

Table 1: Distribution of sex between the two groups

Groups	Female	Male	Total
P+	6	11	17
P-	8	7	15
Total	14	18	P=0.3

P+: patients with proteinuria, P-: patients without proteinuria

Table 2. The comparison of mean serum creatinine (mg/dl) potassium (mEq/L), and Hemoglobin (g/dl) between the two groups, before and after the study.

Lable data	Group	Before study	After study	P value
Serum Cr	P(+)	0.83+0.19	0.99+0.19	0.008
	P(-)	0.83+0.18	0.92+0.22	0.21
	P value	0.97	0.32	
Serum K	P(+)	4.37+0.32	4.4+0.44	0.78
	P(-)	4.49+0.27	4.5+0.40	0.58
	P value	0.26	0.31	
Hb	P(+)	14.12+1.3	13.92+0.99	0.28
	P(-)	14.10+1	12.92+3.3	0.16
	P value	0.96	0.26	

Cr: Creatinine K: Potassium Hb: Hemoglobin
P(+): Patients with Proteinuria, P(-): Patients without Proteinuria

Discussion

Participation of the renin–angiotensin system in erythropoiesis has long been recognized. Angiotensin II directly stimulates erythropoietin production *in vivo* [12,13], and induces the growth of early erythroid progenitors *in vitro*[14], ACE inhibitors and angiotensin II type 1 receptor antagonists have been shown to decrease erythropoietin levels in animals[13,15], in renal transplant recipients with or without post-transplant erythrocytosis[16-18], and in uremic patients[19], In addition, production of interleukin-12[20], and levels of IGF-1[18], cytokines known to induce erythropoiesis, have been shown to be reduced by ACE inhibitors. Along with such observations, it has also been demonstrated in several studies that both ACE inhibitors and angiotensin II type 1 receptor antagonists might contribute to anemia or to a decrease in hemoglobin/hematocrit levels in animals[15,21]as well as in patients with chronic renal failure[22], with renal allografts[16-18], in patients on hemo-

dialysis treatment[23], in hypertension, chronic obstructive pulmonary disease, and congestive heart failure[24]. Also in hypertension, it is noted but in the majority of patients with hypertension, decreases in hematocrit values after renin angiotensin system (RAS) inactivation are limited and are not clinically important[24].

We decided to evaluate the effect of ACE inhibitors such as enalapril on hemoglobin level in diabetic patients with normal renal function. As far as we knew, there was no report on the effect of enalapril on hemoglobin level in diabetic patients with normal renal function.

This study showed that enalapril administration for 3 months to non-azotemic diabetic patients with or without proteinuria, puts no effects on inducing anemia in such patients, also it did not change the level of serum creatinine or serum potassium significantly and there was no difference between male and female patients in these parameters.

As we could not find any significant changes in Hb level caused by enalapril prescription entirely, therefore there was obviously no need to find the relationship between the dose of enalapril and Hb level.

In addition, the decrease in Hb level was not enough (≥ 10%) as described before to diagnose anemia, also it was not necessary to withdraw the drug (for those patients who needed it) and to see the effect of drug withdrawal on Hb level.

There are some reports on the effect of ACE inhibitors on the response of Hb to erythropoietin (EPO) in HD patients. They noted that there was no alteration in the response of Hb to EPO in those patients with or without taking ACE inhibitors[25, 26]. On the other hand S Albitar et al [27] and Schiffl and Lang [28] observed that high dose enalapril [27] and captopril[28] increased the requirement of EPO in HD patients. This study is against our results in normal renal function patients.

Kunihiko Hayashi et al [26] evaluated the effects of ACE inhibitors in hemodialysis patients by measuring the weekly increase in hematocrit (ΔHct) values within 12 weeks of the initiation of rHuEpo treatment. When the ΔHct values were compared directly between the two groups, no effect of ACE inhibitors was observed (P=0.941). They concluded that ACE inhibitors have no effect on the rHuEpo treatment for anemia in hemodialysis patients who were treated with a relatively low dose of ACE inhibitors and low dose rHuEpo. ΔHb in our patients also did not show any significant changes.

It is possible that the drug type (The product manufactured in Iran) is different from other products of this drug in its efficacy and other side effects.

However, most of these studies were done on hemodialysis patients and patients who received rHuEpo. They concluded that low dose ACEIs had no effect on Hb level, though this study was done on normal renal function patients, nonetheless showed the same result.

Conclusion

This study shows that therapy with usual dose of enalapril in diabetics with normal renal function with or without proteinuria, may not induce anemia and this drug can be used without the risk of inducing anemia. We suggest other studies with larger sample size on normal renal function patients and with other ACE inhibitors to evaluate the probable effect of ACE inhibitors on hemoglobin level.

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