Hiroshima J. Med. Sci.
Vol. 47, No.3, 121~124, September, 1998
HIJM 47-18

Effect of the Angiotensin-converting Enzyme Inhibitor Enalapril on Post-transplant Erythrocytosis

Seiji MARUBAYASHI, Hiroyuki YAMAMOTO, Satoshi SHIBATA, Yasuhiro FUDABA, Yoshihiro MIYATA, Kazuyuki FUKUMA, Kazuro OKADA, Takao HINOI, Masahiro IKEDA, Takashi MAEDA, Yoshio OSHIRO and Kiyohiko DOHI

The Second Department of Surgery, Hiroshima University School of Medicine, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan

ABSTRACT

Post-transplant erythrocytosis (PTE) is increasingly recognized as a complication of kidney transplantation. In this study we report the effect of the angiotesin-converting enzyme (ACE) inhibitor enalapril on hematocrit (Ht) and erythropoietin in four patients with PTE. Four renal allograft recipients with Ht greater than 51% were studied. Treatment was initiated with enalapril administered orally at a dose of 2.5 mg/day. All the patients had an increase of hemoglobin (Hb) (17.7 ± 0.64 g/dl), Ht (54.5 ± 1.29 %) and red blood cell count (RBC) (584 ± 19.2 × $10^4/\mu l$). All patients responded to enalapril in 8 weeks with a significant decrease of Hb, Ht, and RBC. In one patient, the downward trend was more rapid and sustained, and treatment had to be discontinued to prevent the development of anemia. Serum erythropoietin showed normal in all four patients and remained unchanged during the study, even after discontinuation of enalapril treatment. Serum creatinine remained relatively stable throughout the study. These results suggest that PTE may not be dependent upon circulating erythropoietin and that enalapril treatment may be an effective treatment of PTE without renal dysfunction.

Key words: *Erythrocytosis, Renal transplantation, Angiotensin converting enzyme inhibitor*

Post-transplant erythrocytosis (PTE) is increasingly recognized as a complication of kidney transplantation[15,17]. We also reported a case of PTE in 1976[18]. Its incidence in renal allograft recipients ranges from 7% to 19%[1,23], and it occurs most commonly in the first 2 years after renal transplant[23]. With the introduction of cyclosporine into clinical practice, an increase in the incidence of PTE was noted in some[23,25], but not all studies[8]. It occurs with well-matched, well-functioning transplants and, although sometimes transient with spontaneous regression, is often persistent[10]. The importance of PTE lies in the increased occurrence of associated thromboembolic events[23,26]. The traditional therapy has been repeated phlebotomy or native nephrectomy[5,23,27]. However, these procedures are often cumbersome for the patients.

Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension and cardiac failure. Based on the observation that ACE inhibition caused anemia in renal transplant recipients[11,14], several groups have used this treatment modality in the management of PTE[2,3,11,12,19]. In this study we report the effect of ACE inhibitor enalapril on hematocrit (Ht) and erythropoietin in four patients with PTE.

MATERIALS AND METHODS

Four renal allograft recipients with Ht greater than 51% were studied. No evidence for secondary polycythemia was found in any of the patients based on clinical features, a pulmonary function test, and transplant ultrasound examinations. The cause of end-stage renal disease was chronic glomerulonephritis in three patients and immunoglobulin A nephropathy in one patient (Table 1). Treatment was initiated with enalapril (Renivase, Banyu, Tokyo, Japan) administered orally at a dose of 2.5 mg/day. All patients were on a standard maintenance immunosuppressive regime of cyclosporine, steroid, and azathioprine, mizoribine or RS 61443. All patients had a stable renal function (mean serum creatinine 1.35 ± 0.25 mg/dl). Arterial blood gas showed O_2 saturation above 96%. No patient had hepatic dysfunction, renal artery stenosis, or iron depletion. Serum erythropoietin was measured by a radioimmunoassay (RIA) using antihuman urine erythropoietin antibody (Mitsubishikagaku kit erythropoietin, RIA). Ht, hemoglobin (Hb), red blood cell count (RBC) and serum creatinine were measured by standard laboratory methods. All data, unless otherwise stated, are presented as means ± SD. Statistical

Reprint requests to Dr. Seiji Marubayashi, The Second Department of Surgery, Hiroshima University School of Medicine, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan

Table 1. Transplant erythrocytosis

No.	Gender/Age	Cause of renal failure	Transplant		Systolic BP/diastolic BP (mmHg)		Erythropoietin (mU/ml)		Side effect
			Type	Duration (months)	Pre-trial	8 weeks	Pre-trial	8 weeks	
1	M/34	IgA nephropathy	LR	25	130/80	124/84	17.5	24.2	anemia
2	M/45	CGN	LR	23	120/90	100/60	34.2	27.6	none
3	M/21	CGN	LR	10	142/78	100/70	14.3	13.1	mild hypotension
4	M/48	CGN	CAD	6	110/70	100/78	11.9	21.5	none

LR: living related renal transplantation, CAD: cadaveric renal transplantation, CGN: chronic glomerulonephritis, BP: blood pressure.

analysis was performed by analysis of variance to compare the experimental groups. Differences were considered to be statistically significant if the p value was less than 0.05.

RESULTS

PTE onset occurs at a median of 16 months after renal transplantation (6 months to 25 months) (Table 1). All the patients had an increase of Hb (17.7 ±0.64 g/dl), Ht (54.5 ± 1.29 %) and RBC (584 ± 19.2 × $10^4/\mu l$) (Fig. 1). The median PTE period prior to enalapril therapy was 9.8 months (1 month to 21 months). One of four patients had mild hypertension requiring calcium channel blocker. All patients responded to enalapril in 8 weeks with a significant decrease of Hb, Ht, and RBC (Fig. 1).

Most patients exhibited a time-dependent drop in Ht as the treatment continued, although the rate and pattern of drop varied. In one patient (No. 1), the downward trend was more rapid and sustained, and treatment had to be discontinued to prevent the development of anemia (Fig. 2). In another patient, treatment was discontinued due to mild hypotension (No. 3). The rate of Ht rebound following the discontinuation of enalapril also varied from patient to patient (Fig. 2). In patient No. 1, in whom Ht was measured within 4 weeks after the discontinuation of treatment, Ht promptly rebounded back within this short interval, while in another patient the recovery was more gradual (No. 3). Serum erythropoietin showed normal in all four patients (19.5 ± 10.1 mU/ml; normal range: 12.5 to 34.5 mU/ml) and remained unchanged during the study (21.6 ± 6.19 mU/ml), even after discontinuation of enalapril treatment. Mean serum creatinine at onset of PTE was 1.35 mg/dl and it remained relatively stable throughout the study (mean Cr; 1.34 mg/dl). No venesections were performed during the study and no thromboembolic episodes occurred.

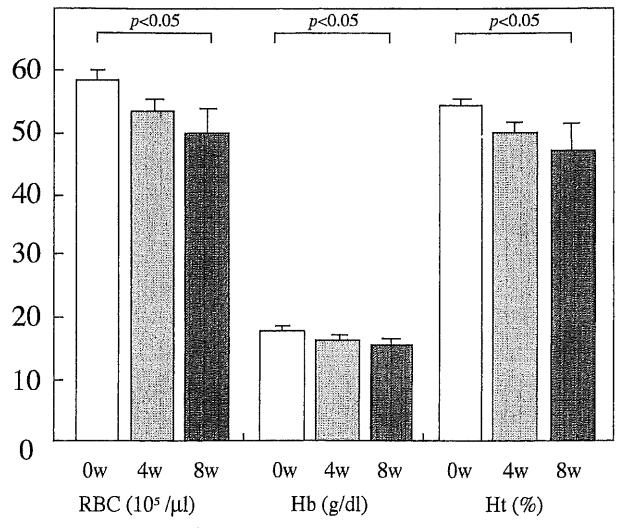

Fig. 1. Evolution of RBC, Hb and hematocrit under enalapril.
Mean reduction in RBC, Hb and hematocrit with treatment in 4 patients.

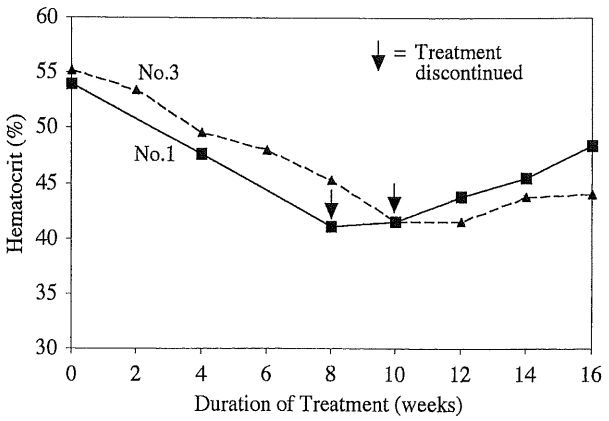

Fig. 2. Patterns of hematocrit response and recovery following treatment with enalapril and discontinuation in patients No. 1 and No. 3.

DISCUSSION

PTE has been reported in association with acute and chronic rejection, renal artery stenosis and hydronephrosis, but in most cases the pathogenesis remains poorly understood. Our study confirms previous reports on the efficacy of ACE inhibition

in lowering the Ht in post-renal transplant patients who developed erythrocytosis[2,3,12]. It is known to occur with well-matched kidneys with good function and higher pre-transplant Ht[10,26]. Some studies suggest that increased circulating levels of erythropoietin are present in PTE.

In the current analysis, PTE occurred most frequently in the first year post-transplant. Wickre et al[26] reporting on 53 patients with PTE noted an incidence of 17.3%, with a mean time of onset post-transplant of 17 months (range 3–90 months). A similar line of evidence was also reported by Glicklich et al[8]. We did not perform red cell mass and plasma volume studies to confirm the presence of true erythrocytosis prior to starting our study. These investigations are not routinely performed on our unit prior to treatment of patients with an elevated Ht. In addition, patients with relative erythrocytosis (stress erythrocytosis) due to reduced plasma volume rather than true erythrocytosis may also have an increased risk of thromboembolic complications and thus treatment is still warranted[2].

Several reports have shown that administration of the ACE inhibitor enalapril to patients with PTE effectively reduced the levels of erythropoietin and Ht[6,12,24]. The mechanism whereby ACE inhibitors decrease the erythropoietin and Ht in patients with PTE is not well known; however, three possible mechanisms are suggested. First, ACE inhibitors have been shown to increase renal plasma flow, thus, the hypoxic stimulus to erythropoietin formation might be diminished. Second, decreased renal oxygen consumption by ACE inhibitors might also reduce the stimulus to erythropoietin production. Third, angiotensin II may exert a direct stimulatory effect on erythropoietin production leading to a reduced formation under ACE inhibition[4,13,27]. Animal studies have shown angiotensin II infusion to cause a rise in plasma erythropoietin levels[16]. Hypoxia and renin cause an increase in erythropoietin levels in rats, which is abolished by an ACE inhibitor but still occurs if angiotensin II is also infused[9]. However, as shown in the present study, there are patients in whom the Ht level decreases after enalapril administration independent of changes in the circulating concentration of erythropoietin. In addition, the Ht level increased again after withdrawal of enalapril with no change in the erythropoietin level. These results suggest that PTE may not be dependent upon circulating erythropoietin. A number of cytokines and growth factors other than erythropoietin have been shown to affect erythropoiesis[7]. Interleukin-3 and granulocyte-macrophage colony stimulating factor have been demonstrated to have stimulatory effects on erythrocytosis[21,22], whereas tumor necrosis factor-α has an inhibitory effect on red-cell precursor proliferation and differentiation which is believed to have an important role in the pathogenesis of anemia associated with chronic inflammatory disease[20]. It is possible that the effect of ACE inhibitors in PTE may be mediated via one or more of these systems, though this remains unproved at present[7].

In summary, we have shown that ACE inhibitor therapy is an effective treatment of PTE without renal dysfunction. However, one patient developed anemia which necessitates frequent monitoring of the Ht during treatment. The exact mechanisms underlying the beneficial effect of ACE inhibitors on PTE should be further investigated.

(Received May 26, 1998)
(Accepted July 30, 1998)

REFERENCES

1. **Aeberkard, J. M., Schneider, P. A. and Vallotton, M.B.** 1990. Multiple site estimates of erythropoietin and renin in polycythemic kidney transplant patients. Transplantation **50:** 613–616.
2. **Beckingham, I.J., Woodrow, G., Hinwood, M., Rigg, K.M., Morgan, A.G., Burden, R.P. and Broughton-pipkin, F.** 1995. A randomized placebo-controlled study of enalapril in the treatment of erythrocytosis after renal transplantation. Nephrol. Dial. Transplant. **10:** 2316–2320.
3. **Danovitch, G.M., Jamgotchian, N.J., Eggena, P.H., Paul, W., Barrett, J.D., Wilkinson, A. and Lee, D.B.** 1995. Angiotensin-converting enzyme inhibition in the treatment of renal transplant erythrocytosis. Transplantation **60:** 132–137.
4. **Fyhrquist, F., Karppinenk, K., Honkanen, T., Saijonmaa, O. and Rosenlof, K.** 1989. High serum erythropoietin levels are normalised during treatment of congestive heart failure with enalapril. J. Intern. Med. **226:** 257–260.
5. **Garvin, P.J., Reese, J.C., Lindsey, L., Aridge, D.L., Domoto, D.T. and Ballal, S.** 1991. Bilateral nephrectomy for post transplant erythrocytosis-indication and results. Clin. Transplant. **5:** 313–317.
6. **Gaston, R.S., Julian, B.A., Barker, C.V., Diethelm, A.G. and Curtis, J.J.** 1993. Enalapril: safe and effective therapy for post transplant erythrocytosis. Transplant. Proc. **25:** 1029–1031.
7. **Gaston, R.S., Julian, B.A. and Curtis, J.J.** 1994. Post transplant erythrocytosis: an enigma revisited. Am. J. Kidney Dis. **24:** 1–11.
8. **Glicklich, D., Tellis, V.A. and Matas, A.J.** 1989. No association between post-transplant erythrocytosis, thromboembolic events, and cyclosporine therapy. Transplant. Proc. **21:** 2141–2142.
9. **Gould, A.B., Goodman, S., DeWolf, R., Onesti, G. and Swartz, C.** 1980. Interrelation of the renin system and erythropoietin on rats. J. Lab. Clin. Med. **96:** 523–534.
10. **Innes, A., Pal, C.R., Dennis, M.J., Ryan, J.J., Morgan, A.G. and Burden, R.P.** 1991. Post-transplant erythrocytosis and immunosuppression with cyclosporine: a case-control study. Nephrol. Dial. Transplant. **6:** 588–591.
11. **Islam, M.S., Bourbigot, B., Codet, J.P., Spongy, B., Fournier, G. and Cledes, J.** 1990. Captoril

induces correction of post renal transplant erythremia. Transplant. Int. **3:** 222–225.

12. **Julian, B.A., Goston, R.S., Barker, C.V., Krystal, G., Diethelm, A.G. and Curtis, J.** 1994. Erythropoiesis after withdrawal of enalapril in post-transplant erythrocytosis. Kidney Int. **46:** 1397–1403.
13. **Kamper, A.L. and Nielsen, O.J.** 1990. Effect of enalapril on haemoglobin and serum erythropoietin in patients with chronic nephropathy. Scand. J. Clin. Invest. **50:** 611–618.
14. **Loftus, W.K., Ierino, F. and Mathew, T.H.** 1988. Enalapril and anemia. Med. J. Australia. **148:** 209–210.
15. **Mulhern, J.G., Lipkowitz, G.S., Brader, G.L., Madden, R.L., O'Shea, M.H., Harvilchuk, H., Guarnera, J.M. and Garmain, M.J.** 1995. Association of post-renal transplant erythrocytoisis and microalbuminuria: Response to angiotensin-converting enzyme inhibition. Am. J. Nephrol. **15:** 318–322.
16. **Nakao, K., Shirakura, T., Azuma, M. and Maekawa, T.** 1967. Studies on erythropoetic action of angiotensin II. Blood **29:** 754–760.
17. **Nankivell, B.J., Allen, R.D., O'connell, P.J. and Chapman, J.R.** 1995. Erythrocytosis after renal transplantation: Risk factors and relationship with GFR. Clin. Transplantation **9:** 375–382.
18. **Ono, E., Nakamura, U., Tanaka, I., Yamane, S., Asahara, T., Yahata, H., Tatsukawa, T., Fukuda, Y., Dohi, K. and Ezaki, H.** 1976. A case of erythrocutosis after renal transplantation. Ishoku **12:** 83–86.
19. **Rostaing, L., Boisseau, M., Durand, D., Huyn, A., Lioveras, J.J. and Suc, J.M.** 1993. Successful treatment of post-transplant erythrocytosis with enalapril. Transplant Proc. **25:** 2325–2326.
20. **Rusten, L.S. and Jacobsen, S.E.** 1995. Tumor necrosis factor (TNF)-alfa directly inhibits human erythropoiesis in vitro: role of p55 and p75 TNF receptors. Blood **85:** 989–996.
21. **Sonoda, Y., Yang, Y.C. and Wong, G.G.** 1988. Erythroid burst-promoting activity of purified recombinant human GM-CSF and interleukin-3: studies with anti-GM-CSF and anti-IL-3 sera and studies in serum free culture. Blood **72:** 1381–1386.
22. **Spivak, J.L., Smith, R.R. and Ihle, J.N.** 1985. Interleukin-3 promotes the invitro proliferation of murine pluripotent haematopoietic stem cells. J. Clin. Invest. **76:** 1613–1621.
23. **Sumarani, N.B., Daskalakiis, P., Miles, A.M., Sarkar, S., Markell, M. S., Hong, J. H., Friedman, E. A. and Sommer, B. G.** 1993. Erythrocytosis after renal transplantation. ASAIO J **39:** 51–55.
24. **Torregrosa, J.V., Campistol, J.M., Montesinos, M., Rodada, A.G., Oppenheimer, F. and Andreu, J.** 1994. Efficacy of captoril on post-transplant erythrocytosis : long-term follow-up. Transplantation **58:** 311–314.
25. **Van Renterghem, Y., Lerut, T. and Roels, L.** 1985. Thromboembolic complications and haemostatic changes in cyclosporin-treated cadaveric kidney allograft recipients. Lancet **1:** 999–1002.
26. **Wickre, C.G., Norman, D.J., Bennison, A., Barry, J.M. and Bennett, W.M.** 1983. Post transplant erythrocytosis : A review of 53 patients. Kidney Int. **23:** 731–737.
27. **Yagisawa, T., Toma, H., Yaguchi, H., Tomaru, M., Iijima, Y., Suzuki, H. and Nakada, T.** 1997. Efficacy of enalapril after ineffective theophylline treatment on erythrocytosis after renal transplantation. Int. Urol. Nephrol. **29:** 363–367.