Angiotensin-Converting Enzyme Inhibitor and Anemia in a Patient Undergoing Hemodialysis

A.	Atsuhiro	Yoshida ^a
K.	Kunio	Morozumi ^a
T.	Tatsuto	Suganuma ^a
J.	Jyoji	Aoki ^a
K.	Kenji	Sugito ^a
S.	Shiro	Nakamura ^a
M.	Midori	Ikeda ^a
T.	Tadashi	Oikawa ^a
T.	Takao	Fujinami ^a
H.	Hirohisa	Kawahara ^b

^aThird Department of Internal Medicine, Nagoya City University Medical School;

^bNagoya Kyoritsu Hospital, Nagoya, Japan

Atsuhiro Yoshida, Third Department of Internal Medicine, Nagoya City University Medical School, 1-Kawasumi Mizuho-cho Mizuho-ku, Nagoya 467 (Japan)

Dear Sir,

Diacid (μg/tnl) 782.9 984.1 382.6 Total (ng/ml) 922.9 1050.2 429.1
577.2 914.5

We have observed a polycythemic patient with poly-cystic kidney disease (PCKD) and hypertension who was treated with enalapril maleate, which is a long-acting angiotensin-converting enzyme inhibitor (ACEI). In this patient, we studied the suppression of erythropoietin (Ep) synthesis by an ACEI.

A 51-year-old man first noted the abdominal tumor in 1978. Included in his family history was the fact that his elder brother and elder sister had PCKD, which is characterized by autosomal dominant heredity and progressive renal failure. He consulted a physician for the abdominal tumor in 1978, and he was discovered to have multiple bilateral renal cysts without hepatic or pancreatic cysts. The diagnosis of PCKD was based on family history and computer-tomographic (CT) findings. In October 1984, he was transferred to our hospital for treatment of chronic renal failure (CRF). He was diagnosed as having end-stage CRF and operated upon for an arteriovenous fistula. His renal function slowly deteriorated. In April 1985, he started hemodialysis (HD) therapy. After HD treatment, his condition improved rapidly and his hematocrit (Ht) increased (18–25%). In 1988, Ht exceeded 40%. Because renal tumor with secondary polycythemia is well known [1], he was examined by CT. There was no difference between the prior study and the follow-up study, which revealed multiple renal cysts occupying the renal parenchyma and no evidence of a malignant tumor. As the concentration of Ep was 86.6 mU/ml and no renal tumor was found, we concluded that the polycythemia was caused by PCKD per se.

In July 1989, his Ht was 48% and his blood pressure (BP) was over 160/95 mm Hg, and he complained of headache. We started enalapril therapy to control the BP and polycythemia. It is a well-known fact that long-term use of ACEI aggravates anemia through the suppression of Ep [2, 3].

After treatment, the concentrations of Ep and aldosterone were rapidly suppressed, the BP went down slowly and the Ht decreased slowly (fig. 1). The level of angiotensin II (A-II) did not change significantly. The level of plasma renin activity (PRA) was tran-

Fig. 1. Clinical findings. Screen shows normal range of Ep. Diacid means diacid metabolite which is the active compound. Total means diacid metabolite and enalapril. siently elevated. There was a positive relationship between Ht and Ep ($Y = 0.0557 X + 38.8$, $r=0.92$).

The concentration of haptoglobin during treatment was 141–159 mg/dl, vitamin B₁₂ 320–370 pg/ml, folic acid 11.9–15.0 ng/ml, and ferritin 20–30 ng/ml. As these tests were within the normal ranges, we ruled out anemia induced by hemolysis or iron deficiency. The serum concentration of the diacid metabolite, which is the active compound of enalapril, was over 300 ng/ml. There was a reciprocal relationship between the diacid metabolite and Ep ($Y = -89.3 X + 4,150$, $r = -0.72$).

In general, a reciprocal relationship between serum Ep levels and Ht has been observed in anemia patients with normal renal function [4]. In patients with end-stage renal failure, levels of Ep were disproportionately low

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when compared to those in patients with normal renal function who had similar Ht levels. The positive correlation between Ht and Ep, which Pavlovic-Kentera et al. [5] reported, indicated that Ep synthesis was not regulated by general hypoxia. PCKD patients manifested higher Ht and Ep levels compared to other kidney disease patients [6], but the cause of the higher Ep in PCKD patients compared to other HD patients is unknown. Some authors have suggested that the renal parenchyma of patients with PCKD might produce greater amounts of Ep due to the ischemia and hypoxia produced by compression from adjacent cysts [7] and increase Ep production in the liver which is a well-known extrarenal Ep production site [8]. Another author reported that renal tumor with secondary polycythemia was well known [1]. In the present case, we excluded renal neoplasm by CT and concluded that the polycythemia was caused by overproduction of Ep due to PCKD per se.

In HD patients, the long-term use of captopril or enalapril aggravates the anemia [2, 3]. In patients with chronic renal failure, clearance of enalapril maleate from the serum is delayed, because renal clearance is the major route of elimination [9], in contrast to captopril. The serum concentration of diacid metabolite which is the active compound of enalapril was over 300 ng/ml, of which at least 10 ng/ml should be achieved to assure maximal blockage of ACE [10].

Onoyama et al. [3] have reported that PRA increased and Ep and A-II were significantly reduced in patients whose Ht was decreased by ACEI. Anagnostou et al [11] concluded that renin and A-II increased the production of Ep by causing vasoconstriction and, consequently, hypoxia. Likewise, the remnant kidney in HD patients is exposed to an hypoxic and anemic milieu, much as in the rat experiment. The ACEI might induce suppression of A-II and Ep [12]. In the present case, we recognized significant suppression of Ep by enalapril and reciprocal relationship between the diacid metabolite and Ep. We presume that the decrease in Ht occurred as a result of suppression of Ep production.

We conclude the following:

In a PCKD patient receiving HD therapy, the positive relationship between Ht and Ep indicated that Ep production was not regulated by general hypoxia.

In HD patients, enalapril therapy should be used with caution, because enalapril suppressed Ep production and induced anemia. In the present case, a reciprocal relationship between the diacid metabolite and Ep was recognized, and this landmark case attests to the suppression of Ep by enalapril.

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