Canine Plasma Erythropoietin Levels in 124 Cases of Anemia

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ABSTRACT. Erythropoietin (EPO) levels in plasma from 124 clinically anemic dogs were determined by *in vivo* bioassay. In 81 anemic dogs with normal renal function, the concentration of plasma EPO showed a close correlation with the hemoglobin concentration. The plasma EPO level was obviously decreased in 43 anemic dogs with renal failure. Of these dogs with renal failure, 17 showed no detectable plasma EPO and resulted in the death of these dogs. In the remaining 26 dogs having detectable plasma EPO, the plasma concentration rate of EPO related to blood urea nitrogen and serum creatinine values.—KEY WORDS: anemia, canine, erythropoietin.
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Erythropoietin (EPO) is a hormone that primarily controls erythropoiesis, and is produced only by the kidneys in dogs [5, 8]. Under anemic conditions, a large amount of EPO is produced, resulting in an acceleration of erythropoiesis in the bone marrow to compensate for decreased red blood cell mass [4]. To determine the plasma EPO level in anemic diseases is therefore important for the pathophysiological understanding of anemia. Since the measurement of the EPO level (international unit : U) has been based on its bioactivity, the EPO level determined by *in vivo* bioassay is supposed to directly indicate EPO activity [1], but there are only a few data on the EPO level in canine plasma measured by *in vivo* bioassay [9]. In this study, the bioactivity of canine plasma EPO was measured by a *in vivo* bioassay in 124 anemic dogs.

Plasma samples were obtained from 124 dogs with anemia at animal hospitals of the University of Tokyo and Kagoshima University. They consisted of 38 hemorrhagic anemias, 32 neoplastic diseases, 21 babesiosis, 13 chronic renal failure (CRF), 13 leptospirosis and 7 other diseases (Table 1). Hemorrhagic anemia was caused by postoperative hemorrhage in 12 dogs, a hemorrhagic condition based on idiopathic thrombocytopenic purpura in 2 dogs, and traumatic hemorrage in 24 dogs. The pathological diagnoses for dogs with neoplastic diseases are shown in Table 2. As to 7 other diseases, there were 3 dogs with pyometra, a dog with autoimmune hemolytic anemia, and 3 dogs with diseases of unknown origin. Of all 124 anemic dogs, 81 dogs had normal renal function and 43 dogs had renal failure. Except for cases of CRF and leptospirosis, anemic dogs with renal failure included 7 hemorrhagic anemias, 8 neoplastic diseases, and 2 other diseases. In all the dogs, the plasma EPO was measured by the polycythemic mouse method [9]. Red blood cell parameters, blood urea nitrogen and serum creatinine were measured simultaneously. As the red blood cell parameters, we determined the red blood cell count with a Micro Cell Counter, the hematocrit value by the microhematocrit method, and the hemoglobin concentration by the cyanmethemoglobin method. The blood urea nitrogen level and serum creatinine level were determined by the Urease-Indophenil method and Jaffe reaction method, respectively.

In anemic dogs without renal failure, the plasma EPO level was closely correlated with the hemoglobin concentration in all cases of hemorrhagic anemia (31 dogs), neoplastic diseases (24 dogs) and babesiosis (21 dogs) (Fig. 1). There were no significant statistical differences between these groups in regressions. Data for 5 anemic dogs with other diseases were plotted within either

Table 1. Causes of anemia in 124 dogs associated with or without renal failure

Causes of anemia	with RF[a)]	without RF	Total
Hemorrhage	7	31	38
(Postoperative)	(4)	(8)	
(ITP[b)])	(—)	(2)	
(Trauma)	(3)	(21)	
Neoplasia	8	24	32
Babesiosis	—	21	21
CRF[c)]	13	—	13
Leptospirosis	13	—	13
Other Causes	2	5	7
(Pyometra)	(1)	(2)	
(AIHA[d)])	(—)	(1)	
(Unknown)	(1)	(2)	
Total	43	81	112

a) Renal failure.
b) Idiopathic thrombocytopenic purpura.
c) Chronic renal failure.
d) Autoimmune hemolytic anemia.

Table 2. Pathological diagnosis of 32 neoplastic cases

Histopathological diagnosis of neoplasia	Numbers of dogs
Mammary Gland Tumor	5
Malignant Lymphoma	7
Malignant Melanoma	2
Osteosarcoma	2
Testicular Tumor	4
Ovarian Tumor	3
Squamous Cell Carcinoma	3
Mast Cell Tumor	2
Hepatoma	1
Pulmonary Tumor	2
Hemangiosarcoma	1
Total	32

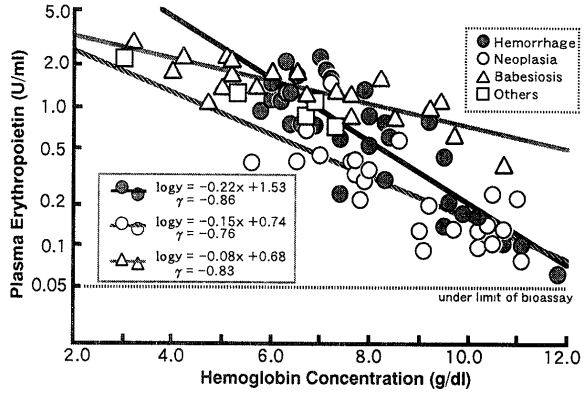

Fig. 1. Relationship between hemoglobin concentration and plasma erythropoietin value in anemic dogs without renal failure: 31 hemorrhagic anemias, 24 neoplastic diseases, 21 babesiosis and 5 other anemic diseases. Regression equations were established for three groups.

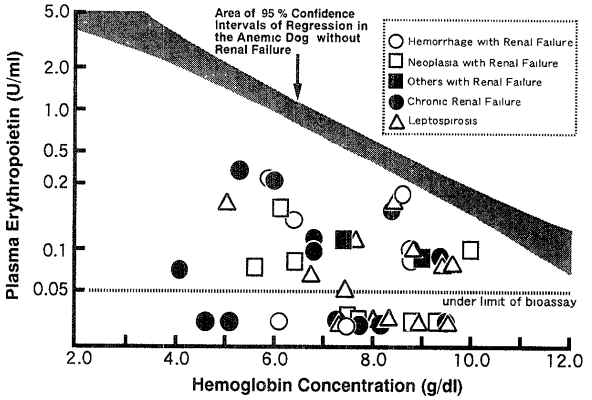

Fig. 2. Relationship between hemoglobin concentration and plasma erythropoietin value in anemic dogs with renal failure: 13 chronic renal failures, 13 leptospirosis, 7 hemorrhagic anemias, 8 neoplastic diseases and 2 other anemic diseases. In these 43 dogs, the plasma erythropoietin level was decreased and each value was plotted out of the area of 95% confidence intervals of regression in anemic dogs without renal failure showed in Fig. 1. In 17 dogs, plasma erythropoietin values were undetectable.

confidence area of these regressions. The regression equation, log y= −0.18x + 1.16 was obtained with a correlation coefficient of −0.81 for all 81 anemic dogs. In human beings, similar results have been reported [2, 11]. In our previous study, we determined plasma EPO bioactivities of experimentally anemic dogs with normal renal function, in which anemia was made by phlebotomic treatment and plasma EPO was measured by *in vivo* bioassay [10]. In this study, plasma EPO bioactivities of clinically anemic dogs were made clear.

In all 43 anemic dogs with renal failure, plasma EPO values were low, and were plotted below and out of the confidence area of anemic dogs without renal failure (Fig. 2). No correlation could be found between the plasma EPO value and the hemoglobin concentration in both groups of CRF (13 dogs) and leptospirosis (13 dogs). This low plasma EPO level in dogs with renal failure was previously demonstrated by radioimmunoassay [6], but plasma EPO bioactivities of dogs with renal failure were determined in this study for the first time. These low plasma bioactivities were similar to those for the serum level reported in dogs with renal failure [6]. Additionally, 17 of 43 dogs with renal failure had no detectable plasma EPO in spite of severe anemia, and all of them died. This result was thought to be of some help in making a prognosis for these anemic dogs with renal failure.

In 26 anemic dogs with renal failure, in which plasma EPO could be detected, each plasma EPO value was compared with that of the anemic dogs without renal failure. The concentration of plasma EPO was estimated from the mean plasma EPO value for anemic dogs with normal renal function, contrasted with the above-mentioned regression equation for 81 anemic dogs. These plasma EPO concentrations in anemic dogs with renal failure appeared correlated to their blood urea nitrogen and serum creatinine values (Fig. 3). In general, it is known that the hematocrit value correlates with the blood urea nitrogen value in anemic humans associated with renal failure [3, 7]. However, no significant relationship between the blood urea nitrogen level (or serum creatinine level) and the plasma EPO level has been reported.

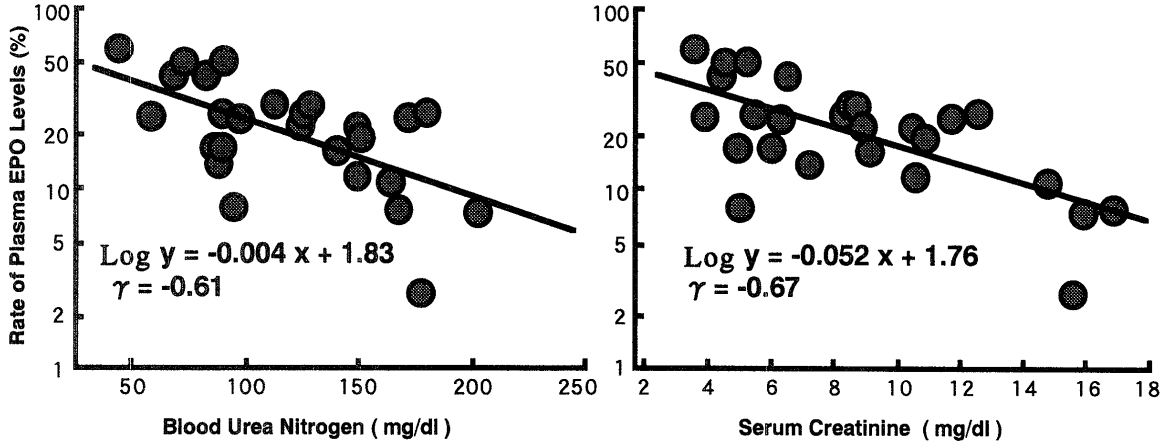

Fig. 3. Concentrations of plasma erythropoietin in 26 anemic dogs with renal failure in which plasma erythropoietin could be detected by *in vivo* bioassays. These erythropoietin values are possibly related to blood urea nitrogen and serum creatinine.

A prospective study on the relationship between EPO production in the kidney and the severity of renal failure will require additional investigation.

The present results indicate that there was a high correlation between hemoglobin concentrations and plasma EPO values in dogs with various anemic diseases, and that the plasma EPO level corresponded with the degree of anemia. Additionally, the plasma EPO level in anemic dogs with renal failure was at a low level, which indicated a close relationship with the severity of renal function. It may be possible to make the prognosis on the basis of the plasma EPO value.

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