Preventive Effects of Recombinant Human Erythropoietin Administration on Anemia Associated with Repeated Hemodialysis in Nephrectomized Dogs

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ABSTRACT. The preventive effects of recombinant human erythropoietin (rEPO) administration on progression of anemia were evaluated during hemodialysis in nephrectomized dogs. In control dogs given no rEPO, anemia gradually progressed with repeated hemodialysis and with little erythropoietic response observed in the bone marrow. In dogs administered with rEPO, however, an active erythropoietic response was induced in the bone marrow, indicating that anemia due to hemodialysis was being prevented.—key words: canine, erythropoietin, hemodialysis.


Pharmaceutical erythropoietin (EPO) has been reported to be effective on anemia for many human anemic patients with renal failure[2, 3, 5, 6, 12]. In small animal medicine, EPO preparations have recently been used, but its effects on dogs with renal failure have not been studied thoroughly. When such dogs are treated with hemodialysis, the anemic condition is further aggravated by loss of red blood cells through dialytic treatments or other causes [1, 7]. Under such conditions, the preventive effect of EPO administration on anemia need to be assessed in detail. In this study, the effect of EPO administration was studied using hemodialysed nephrectomized dogs. The prevention of anemia caused by dialytic treatment was evaluated through the examination of erythropoietic responses in the bone marrow in addition to peripheral red blood cell mass.

Six male and six female healthy adult mongrel dogs weighing 9.0–15.0 kg were used. All the animals were kept alive by hemodialysis after a bilateral nephrectomy. The nephrectomy was performed under OF inhalation anesthesia, and silicon external shunt tubes for hemodialysis were also installed into the left jugular vein and artery. Following the nephrectomy, a total of five supportive hemodialysis treatments, each lasting for 2 hr, were performed at 24-hr intervals using the small animal hemodialysing system (NBM-100, Senko Medical Instrument, Tokyo). Intercircuit blood flow was maintained within 4–6 ml/kg/min during the hemodialysis. Blood was accessed by an external A-V shunt, and a holofiber dialyzer column supplied 0.8 m² of dialysing area. Six control dogs given no EPO administration were used to monitor the development of anemia caused by hemodialysis, and six dogs treated with EPO were used to evaluate the prevention effect of this drug upon anemia. Recombinant human EPO (rhEPO; epoetin beta, Chugai Seiyaku, Tokyo) was administered at a dosage of 100 U/kg intravenously following hemodialysis. This dosage was chosen on the basis of our previous reports [10, 11]. Blood sampling and bone marrow aspiration were carried out every 24 hr and were analyzed hematologically (red blood cell count, hemoglobin concentration, hematocrit value and white blood cell count) and biochemically (plasma total protein, blood urea nitrogen, serum creatinine, sodium, potassium, chloride, calcium and inorganic phosphorus).

As shown in Fig. 1, there were no significant differences in the levels of blood urea nitrogen, serum creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, white blood cells or plasma total protein, between the control and the rhEPO administered groups. It was shown that the dialytic efficiency and the blood concentration or dilution effect [1] in the hemodialytic treatment were similar in all the experimental dogs.

In the control group, given no rhEPO, anemia progression was evident as judged by the red blood cell count, hemoglobin concentration and hematocrit value (Fig. 1). The mean red blood cell count through the first, second, third, fourth and fifth hemodialysis decreased 7.5, 14.7, 6.7, 5.1 and 6.0% of pre-hemodialytic value, respectively. The mean reduction rate in all the 5 times was 8.1%. In the same manner, the mean reduction rate of the hemoglobin concentration and hematocrit value was 7.9 and 8.0%. From these results, the loss of red blood cells in each hemodialysis was estimated as about 8%. Despite the anemia progression, little erythropoietic response was noticed in the bone marrow myeloid:erythroid ratio. Since the kidney is the only organ known to produce EPO in the dog [8, 9], these inactive erythropoietic responses in the bone marrow were possibly a result of inadequate endogenous EPO caused by the bilateral nephrectomy.

In the rhEPO administered group, the reduction of red blood cells was mitigated and was significantly different from that of the control group (Fig. 1). While the loss of red blood cells should be the same in all the experimental dogs, the red blood cell mass in the dogs administered rhEPO was maintained within the normal range, i.e. the red blood cells lost through hemodialytic treatments were supplemented by newly produced red blood cells. Activated erythropoiesis, following rhEPO administration, was indicated in the bone marrow myeloid:erythroid ratio (Fig. 1), which accounted for the new production of red blood cells.

As shown in this study, rhEPO administration has a sufficient preventive effect on anemia caused by red blood cell loss in dialysed nephrectomized dogs. In dogs, this pharmaceutic EPO should be useful for treating anemia associated with renal failure [4, 8], and due mainly to
deficiency of endogenous EPO production, particularly, rhEPO administration may lessen the need for blood transfusion [1, 4].

REFERENCES