Anaphylactic Reaction to Recombinant Human Erythropoietin

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Dear Sir,

Erythropoietin is a 166 amino acid glyco-protein hormone which regulates the rate of proliferation and differentiation of erythroid precursors in bone marrow [1]. It is primarily synthesized in the kidney in response to anemic or hypoxic hypoxia [2]. The recombinant product has the same composition of amino acids as natural human erythropoietin [3]. As it has both a protein component and antigenic capability, it could, at least theoretically, give rise to immunological response. Although several studies have underlined the absence of anti-erythropoietin antibodies (Ab anti-rHuEPO) [1, 3, 4], recent publications have mentioned the detection of these antibodies in patients resistant to medicine, without any other reasons which could explain this lack of response [5].

We had the opportunity of studying a relevant case in our hemodialysis program. The patient presented a severe anaphylactic reaction attributable to rHuEPO. He was a 28-year-old man treated by hemodialysis (HD) since 1978 for chronic renal failure (CRF) due to reflux nephropathy. He required approximately 1 blood unit transfusion monthly. He had no predisposing atopic antecedents, nor any allergic reactions to medicines or blood derivatives. In September 1991, treatment with rHuEPO (Erantin, Boehringer Mannheim, FRG) was initiated for anemia (40 U/kg body weight intravenously 3 times weekly after HD session) with good hematological response and no intolerance. Maintenance dose was 30 U/kg 3 times a week, and serum hematocrit level was maintained in the 30-35% range. No further transfusion was required. The HD regime was 12 h per week (3 sessions) with bicarbonate dialysis solution and gamma-ray-sterilized cellulose triacetate membrane (Baxter CT-110G). The patient was treated with a multivitamin preparation, calcium carbonate and atenolol.

In March 1992, at the end of an HD session and immediately after the initiation of rHuEPO infusion, he suffered bronchospasm, cyanosis, swelling of the face and hypotension. He presented no fever, shivering, or cutaneous eruptions. rHuEPO infusion was terminated, face
mask oxygenation was begun at 0.4 FiO$_2$ and 0.5 cm$^3$ of 1:1,000 epinephrine was administered subcutaneously, together with 200 mg of intravenous hydrocortisone. The symptoms progressively remitted, and the patient had recovered totally and was asymptomatic 3 h from the start of the episode.

Posterior studies showed: (A) Prick test and sequential intradermal reaction with increasing doses of rHuEPO (0.1/1/10/100/1,000 U per ml) gave negative results. (B) Peripheral eosinophil count was 210/mm$^3$. Eosinophil counts prior to the episode were also normal. (C)$\text{IgE}$ serum concentrations showed moderate elevation at 404 U/ml. No prior basal data were available. (D) The presence of IgE antibodies to rHuEPO was detected using material supplied by RAST (Pharmacia-Sweden). The antigen was obtained from a commercial rHuEPO preparation (Erantin 1,000 U/ml) following the Ceska modified method [6]. (E) Three blood cultures, as well as a culture of the material used in dialysis were negative.

It is probable that the introduction of rHuEPO as a clinical treatment is the most important development to have taken place during the past decade in the therapeutic management of uremic patients.

Treatment with rHuEPO is sometimes associated with side effects. These include hypertension, hypertensive encephalopathy, hyperkalemia, fistula clotting, flu-like syndrome and others of lesser importance [1, 7-9]. Nevertheless, we have not found any reference in the literature relating this medicine to hypersensitivity reactions.

In our patient, we can assume an anaphylactic reaction to rHuEPO, as the reaction took place during intravenous administration of the drug. We also detected anti-rHuEPO-specific IgE. The patient continued under the same treatment and dialysis therapy, except that rHuEPO was not given without new reactions presenting.

Schroeder-Kolb et al. [10] described papulous cutaneous eruptions in some patients during the first months of treatment which evolved to spontaneous resolution. Administration of the drug only had to be withdrawn in 1 case. Nevertheless, other authors such as Grutzmacher et al. [11] found no problems of local intolerance using intracutaneous testing, carried out with a dose of 20 U of rHuEPO before the first intravenous application, except in 1 patient, in whom a slight early reaction was observed. In spite of this, the patient tolerated intravenous therapy without any reaction. It is also known that a negative cutaneous test for immunoreaction does not exclude intravenous intolerance.

Now that the use of rHuEPO is becoming more widespread for the treatment of anemia in patients receiving HD, those with advanced CRF, and for other types of anemia, we believe that the detection of this side effect should be published as, although anti-rHuEPO antibodies have already been described, the clinical response of our patient was completely unique. The possibility of an-aphylactic reaction due to anti-rHuEPO-specific antibodies with a life risk for the patient must be kept in mind.

References


