

ERYTHROPOIETIN IN SURGERY

E. Baudoux (1), M. Janssens (2), Y. Beguin (3), D. Sondag (1), G. Fillet (3), M. Lamy (2).

(1) Blood Transfusion Centre Liège, Belgian Red Cross, Belgium.

(2) University Hospital of Liège, Department of Anaesthesiology, Belgium.

(3) University Hospital of Liège, Department of Hematology, Belgium.

PHYSIOLOGY¹

Erythropoietin (EPO) is a 34000 Dalton glycoprotein hormone produced for 90 % by the kidney. EPO secretion occurs in response to hypoxic stimuli such as a decrease in circulating red cell volume, low O₂ hemoglobin saturation, low blood flow in renal artery, by a regulatory process responding to a low O₂ concentration in the renal vein.

EPO is active on the erythropoietic lineage of the bone marrow, with a mitogenic effect on BFU-E, CFU-E, proerythroblasts and basophilic erythroblasts. Moreover, EPO also increases the rate of differentiation of CFU-E into proerythroblasts.

EPO elimination is essentially made by the hormone target cells, but a small part of it can be found in the urine.

Serum EPO levels, as detected by RIA or ELISA methods, have to be analyzed in relation to the hematocrit (Hct). In all types of anemia a slow increase in serum EPO concentration can be observed until Hct decreases to about 38 %, and below this point EPO increases exponentially. In some situations EPO can augment in an appropriate manner but with no relation to the actual Hct (respiratory failure, congenital cardiopathy, high affinity hemoglobin). The opposite can also occur, with a low EPO level, inadequate for the degree of anemia, for instance in chronic renal failure, post-nephrectomy, chronic disorders (rheumatoid arthritis, AIDS), or in some malignant diseases.

PHARMACOLOGICAL USE OF EPO

Bioengineering techniques have made large amounts of recombinant EPO production, available for clinical use since about 1985.

Routes of Administration:²

The most utilized routes to administer EPO are subcutaneous (SC) and intravenous (IV) routes, each possessing particular kinetics, advantages or disadvantages. Compared with SC, the IV route produces higher plasmatic EPO concentrations and bioavailability, and a larger area under the curve of concentration vs time, but a faster disappearance from circulation. In contrast, EPO requirements to obtain the same clinical effect are 50 to 60 % lower in patients treated SC. These facts indicate that SC kinetics is better than IV because of lower peak concentrations and longer residence time of EPO in human plasma, which are closer to the physiological profile of the hormone.

Clinical Use

The indication of choice of recombinant human EPO is the treatment of the anemia of patients with chronic renal failure on dialysis. Usual doses are 40-100 U/Kg SC, three times weekly. The dose must be adjusted until a target hematocrit is obtained (usually 30%). Side effects are rare but are seen with high doses which can cause hypertension even accompanied by seizures. These reactions appear to be due to the hemodynamic adaptation to an increasing circulating red cell mass. Rare instances of thrombosis of the arteriovenous fistula have been described but this has been attributed to a quick increase in Hct and/or blood viscosity³. The use of EPO has made it possible to cease transfusions in these patients, avoiding transfusion-associated risks of viral disease transmission, sensitization, and iron overload. Particular attention must be paid to correcting iron or vitamin carency, aluminum intoxication, hyperparathyroidism, and to the treatment of any infectious disease. These situations may lower the response to EPO administration^{3,4}.

Other therapeutic applications could be mentioned, as the treatment of the anemia of patients with renal failure, but not on dialysis, in whom EPO seems to correct the anemia without altering the renal function. Other studies have also demonstrated that larger doses of EPO are able to correct the anemia in patients with malignant diseases, AIDS or rheumatoid arthritis.

APPLICATIONS IN SURGERY AND AUTOTRANSFUSION

We reviewed published studies and case reports on the possible use of EPO in perisurgical situations, with or without autologous blood (AB) donation. In patients in which neither AB nor homologous blood (HB) transfusion are possible, EPO given preoperatively seems to contribute to increase the circulating red cell mass prior to surgery, reducing the probability of red cell transfusions. Data about the postoperative use of EPO seem to be insufficient for the moment, but studies are ongoing and the results will probably be available in a short time.⁴

For patients included in AB predonation programs, the following arguments can help to understand the possible role of EPO treatment as a complementary approach. First of all, it is quite clear that some percentage of the patients in AB donation programs do not complete their procedure because of anemia, and that these patients have a higher probability to receive HB in their perioperative period. This probability is estimated at 13 % in patients who donated the amount of blood requested by the surgeon, and at 43 % in patients who did not⁵. The reason why some patients do not have a sufficient amount of AB at the end of the predonation procedure is that the hematopoietic response to iterative phlebotomy is too slow to reconstitute the initial Hb level before surgery, and that a sufficient EPO secretion occurs only for a certain degree of anemia, incompatible with ambulatory predonation procedure^{6,7}. These patients are often characterized by lower iron stores, and by a lower initial Hct^{4,5}.

In studies in which EPO is given during predonations, procedures are significantly more successful than in patients receiving placebo. EPO doses necessary in this setting vary from 100 U/Kg daily⁸ to more than 600 U/ Kg two or three times weekly⁴.

First of all, EPO therapy, in addition to AB collection, was effective to increase the amount of blood collected, in terms of total red cell volume as well as of the number of units obtained. In the main published study⁴, the number of patients unable to give 4 units or more was reduced from 29 % in the placebo group to 4 % in the EPO group. On the other hand, patients who received EPO seem to be at a lower risk of exposure to HB in the perioperative period.

Another issue for these studies was to try to identify the patients for whom EPO treatment would be most beneficial, and some conclusions can be made. Patients who are scheduled to predonate large volumes of blood (>4 units) and are treated with EPO seem to be in better pre surgical condition (in terms of hemoglobin or Hct) than patients who only receive iron supplements. Moreover, the increase in red blood cell production induced by EPO and the mobilization of stored iron could lead anemic patients to be enrolled into AB predonation protocol despite the fact that their initial parameters are non suitable³, provided they are given adequate iron supplements.

All patients included in AB predonation protocols with EPO should receive iron, orally or sometimes IV⁶. This is necessary to achieve a sufficient iron supply to the bone marrow coming from both the reticuloendothelial system and the iron therapy. In the same way, iron supplements should be given to patients undergoing an AB predonation program, with or without EPO, especially to premenopausal women. For a routine use, the oral route is of course the simplest and the best in terms of side effects^{9,10}.

The side effects of EPO are well-known and have mostly been seen in patients with renal failure. In published papers, patients with contraindications or in conditions known to be associated with poor response to EPO were excluded. No side effect was considered as EPO-dependent. In opposition to what happens in patients with renal failure, no significant change was noticed in arterial blood pressure. However, it remains necessary to fully assess the safety of EPO in perisurgical conditions.

IS EPO OF INTEREST FOR USE IN SURGERY AND/OR AUTOTRANSFUSION?

In order to lower HB exposure to surgical patients, several methods can be used. In a "blood sparing " policy, AB predeposit, combined with peroperative blood saving techniques can avoid many HB transfusions. In many cases, this reduction still remains unsatisfactory, because of the insufficient use of these techniques. The question of optimizing a global blood saving policy has to be continuously reviewed, to insure the most favorable attitude at any time.

However, the routine procedures used in AB predeposit do not ensure that all patients will receive only AB. In these cases, it seems to be interesting to use a technique that stimulates red cell production and improves the rate of AB collections.

The cost-effectiveness of this approach could also lead to future recommendations of reserving EPO only to well-targeted patients, who could receive a maximum benefit from it.

In summary in accordance with other authors¹¹, we think that EPO has a role in limiting HB exposure in patients who have to donate a large number of AB units, especially if the collection period is limited. On the other hand, patients having lower Hct at the start of a predeposit procedure, could also be selected to receive EPO in order to insure an optimal collection to obtain the number of units ordered by the surgical team.

BIBLIOGRAPHY:

- ¹ ERYTHROPIETINE: UTILISATION DIAGNOSTIQUE ET THERAPEUTIQUE**, Y. Beguin, G. Fillet, in *Revue Médicale de Liège* 35: 261-267, 1990.
- ² SINGLE DOSE KINETICS OF RECOMBINANT ERYTHROPIETIN AFTER INTRAVENOUS, SUBCUTANEOUS AND INTRAPERITONEAL ADMINISTRATION**, D. Kampf, A. Kahl, et al. in *Erythropoietin: from Molecular Structure to clinical Application*, Contributions to Nephrology, Basel, Karger, 76: 106-110, 1989.
- ³ POTENTIAL ROLE OF RECOMBINANT ERYTHROPIETIN IN THE PERI SURGICAL SETTING**, L. T. Goodnough, *International Journal of Cell Cloning*, 8 : 203-210, 1990.
- ⁴ THE ROLE OF RECOMBINANT ERYTHROPIETIN IN HOMOLOGOUS TRANSFUSION AVOIDANCE**, J. T. Sobota, in *Erythropoietin in Renal and Non-Renal Anemias*, Contributions to Nephrology, Basel, Karger, 1991, 88: 334-348, 1991.
- ⁵ INCREASED PREOPERATIVE COLLECTION OF AUTOLOGOUS BLOOD WITH RECOMBINANT ERYTHROPIETIN THERAPY**, L. T. Goodnough et al., *The New England Journal of Medicine*, 321: 1163-1167, 1989.
- ⁶ LIMITATIONS OF ERYTHROPOIETIC RESPONSE TO SERIAL PHLEBOTOMY: IMPLICATIONS FOR AUTOLOGOUS DONOR PROGRAMS**, L. T. Goodnough et al., *J Lab Clin Med*, 155: 29-35, 1990.
- ⁷ PHYSIOLOGICAL RESPONSE TO PHLEBOTOMIES FOR AUTOLOGOUS TRANSFUSION AT ELECTIVE HIP-JOINT SURGERY**, G. Birgegard et al., *Eur J Haematol*, 46: 136-139, 1991.
- ⁸ AUTOLOGOUS BLOOD TRANSFUSION WITH RECOMBINANT ERYTHROPIETIN IN HEART OPERATIONS**, Y. Watanabe et al., *Ann Thorac Surg*, 51:767-72, 1991.
- ⁹ IRON-RESTRICTED ERYTHROPOIESIS AS A LIMITATION TO AUTOLOGOUS BLOOD DONATION IN THE ERYTHROPIETIN-STIMULATED BONE MARROW**, L. T. Goodnough et al, *J Lab Clin Med*, 118: 289-296, 1991.
- ¹⁰ THE EFFECT OF IRON SUPPLEMENTATION ON ERYTHROPOIESIS IN AUTOLOGOUS BLOOD DONORS**, D.H. Biesma et al., *Transfusion*, 32: 162-165, 1992
- ¹¹ INCREASING AUTOLOGOUS BLOOD DONATION WITH RECOMBINANT HUMAN ERYTHROPIETIN**, E. A. Levine, in *Erythropoietin in Renal and Non-Renal Anemias*, Contributions to Nephrology, Basel, Karger, 88: 327-333, 1991.