Influence of Recombinant Erythropoietin on the Production of Endothelin-1 from Human Umbilical Artery

M.	Michele	Buemi ^a
N.	Nancy	Morabito ^a
S.	Salvatore	Palella ^a
A.	Alessandro	Allegra ^a
N.	Nicola	Frisina ^a
M.	Maria	Gemelli ^b
R.	Rosa	Manganaro ^b
L.	Lorenzo	Stelitano ^b
A.	Antonia	Palmara ^b

^aCattedra di Nefrologia II, Dipartimento di Medicina Interna, ^bCattedra di Neonatologia, Università di Messina, Italy

Prof. Michele Buemi, MD, Via Oddo delle Colonne 16, I-98100 Messina (Italy)

Dear Sir,

Induced hypertension due to treatments with recombinant erythropoietin (rHuEPO) is with no doubt the most frequent and important side effect of this hormone therapy, capable of conditioning the therapeutic success in subjects affected by anemia from renal failure.

Although different factors, among which the increase in hematic viscosity, are recognized as possibly responsible for the pressure rise which often goes along with rHuEPO treatment, up to now a reliable explanation of the pathogenetic mechanisms of hypertension induced by erythropoietin [1] is still missing. In previous investigations, through the evaluation of the changes brought about by the intravenous administration of rHuEPO on the pretibial flux by means of the Xenon 133 clearance, we showed the existence of a direct vasoconstrictive action exerted by erythropoietin on the compliance vasa [2]. The presence of endothelial receptors for the erythropoietin could give account of such action [3]. Furthermore, in our previous investigations as well as in other investigations [4], it was shown how the intravenous chronic treatment was able to change the plasma levels of endothelin-1, a substance produced by the endothelium, able to induce a high vasoconstriction. Yet, the plasma dosage of endothelin does not seem to correspond to the real activity of the basal endothelium. Therefore, we wanted to use an experimental model based on the umbilical arteries, where the receptors for endothelin are to be found [5]. The arteries were quickly Fig. 1. Production of immunoreactive endothelin-1 (ir ET-1) in the umbilical artery: electrolytic solution (I); rHuEPO solvent (II); 30 U of rHuEPO (III).

20 µl of solvent. Then, the 3 umbilical artery segments were kept for 10 min at 37°C, were weighed and the corresponding supernatant frozen at -30°C, the endothelin-1 was dosed with the RIA method (Amersham, UK). The results obtained from 25 umbilical arteries showed the presence of a significant increase in the concentration of endothelin-1 from the medium to

which rHuEPO was added (fig. 1). Results are expressed as means $\pm$ SE and Student's test was performed for all comparisons. Therefore, our study seems to confirm the possibility that the vasoconstrictive action played by erythropoietin might be caused by the stimulus exerted by the hormone on the endothelial cells to make them produce endothelin-1.

isolated from umbilical cords from neonates of nonhypertensive mothers with the purpose of evaluating the rHuEPO action on the production of endothelin-1. Our method consisted in taking, soon after a natural delivery, 10 cm of the median part of the umbilical cord from which we immediately isolated the umbilical artery by means of a stereo microscope which was divided into 3 2-cm long segments. The 1st segment (I) was put in 1 ml of cold buffered electrolyte solution (4°C), the 2nd (II) was kept in a medium with buffered electrolyte solution plus 20 μ l of rHuEPO solvent (human serum albumin 2,5 mg/ml; sodium 160 mM; chlorides 100 mM; citrate 20 mM), the 3rd (III) was put in 1 ml cold buffered electrolyte solution and 30 U of rHuEPO with

©1993 S. Karger AG, Basel

0028-2766/93/

O641-0165\$2.75/0

To sum up, our findings seem to confirm the possibility that various growth factors and cytokines may play an important effect on the regulation of the vascular tone – as it was also shown through the increase induced by interleukin-1 on the production of prostacyclins and nitric oxide [6]. Further investigations are required to better identify the vasoconstrictive mechanisms of recombinant erythropoietin and its action on all the factors able to modify the vascular reactivity.

References

Schafer RM, Horl WH, Massry SG: Treatment of renal anemia with recombinant human erythropoietin. *Am J Nephrol* 1989;8:352-362. Buemi M, Allegra A, Marino D, et al: Erythropoietina ricombinante ed ipertensione arteriosa. *G Ital Nefrol* 1991;8:155-160. Anagnostou A, Lee ES, Kessimian N, Levinson R, Steiner M: Erythropoietin has a mitogenetic and positive chemotactic effect on endothelial cells. *Proc Natl Acad Sci USA* 1990;87:5978-5982.

Tkayama K, Kinugasa E, Akizawa T, Koshi-kawa S: Effects of recombinant human erythropoietin on blood coagulation, fibrinolysis and endothelium in hemodialysis patients. *Blood Purif* 1991;1:53-54.

Clozel M, Fischli W, Guilly C: Specific binding of endothelin on human uteroplacental arteries. 7th World Congr Hypertens Pregnancy, Perugia, 1990.

Mantovani A, Dejana E: Cytokines as communication signals between leukocytes and endothelial cells. *Immunol Today* 1989; 10: 370-373.

Buemi/Morabito/Palella/Allegra/Frisina/ Gemelli/Manganaro/Stelitano/Palmara
Erythropoietin and Endothelin-1