Effect of Intravenous Recombinant Erythropoietin Administration on Plasma and Erythrocyte Magnesium Concentrations in Patients on Hemodialysis

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Table 1. Plasma and erythrocyte magnesium concentrations before and after i.v. rHuEPO administration in healthy subjects and hemodialyzed patients

Dear Sir,

Erythropoietin is the main regulator of erythropoiesis, and its effect on the mitotic activity of erythroid precursors leads to an important modification in the ionic intracellular content. It has been observed that erythropoietin may first act by modifying the cationic flow. When calcium was chelated in the culture medium and in the cell cytoplasm it was in fact found that calcium is fundamental in allowing the hormone to link to the target cells. The entrance of calcium into the cell and the formation of gradients between its cytoplasm and nucleus appear to be crucial moments in the triggering of replication kinetics [1].

Many other growth factors and different cytokines have the same effect as erythropoietin on the intracellular ions. By utilizing the Gardos effect, we demonstrated elsewhere that many GFs behave like ionophoric substances toward calcium ions, determining a significant Ca-dependent effusion of K⁺ from the cells studied [2].

However, although the effect of erythropoietin on Ca²⁺ has been studied in depth, to our knowledge few data are available in the literature on the relationship between the erythropoietic hormone and other ions, even if it is known that the modification of the concentrations of cations is one of the events triggering RNA synthesis. Here the relations between erythropoietin and magnesium ions are practically unknown.

It has been found that in cancer patients on cisplatin the response to recombinant erythropoietin (rHuEPO) given for anemia caused by chemotherapy is correlated with magnesium serum concentrations [3].

However, it is not known whether this correlation depends on the real effect of magnesium on the production or on the activity of erythropoietin, or rather is linked to ne-phropathy from cisplatin, which is known to be magnesium dependent.

The effects of erythropoietin on magnesium behaviour are even less well understood.

Therefore, also in view of experimental evidence (obtained by using 28Mg) of an increase of the entrance of ions to within the

cells in the early stages of erythropoiesis [4], we made a comparative study of the effects of i.v. rHuEPO on plasma and erythrocyte magnesium concentrations in healthy controls and patients receiving hemodialysis for chronic terminal renal failure.

The study was conducted on 14 Caucasians after having obtained their informed consent: 7 healthy volunteers (4 men, 3 women; mean age 54 ± 9 years) made up the control group and 7 (4 men, 3 women; mean age 51 ± 6 years) had chronic terminal renal failure (2 nephroangiosclerosis, 3 glomerulo-nephritis, and 2 polycystic kidneys) and underwent hemodialysis three times a week, were not anephric, and were age and sex

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matched to the control group. Blood samples were taken in the morning from the subjects who were fasting and after a 12-hour rest. In the hemodialytic patients, samples were obtained during the intervals between dialysis.

All subjects were administered rHuEPO (10,000 U, i.v. bolus in the cubital vein of the arm), and blood samples were drawn 0, 15, 30, 60 and 90 min afterwards for the measurement of plasma and erythrocyte magnesium. The sample was assayed in a single sitting using atomic absorption spectrometry.

Statistical analysis was performed using Student's t test for paired data. Values of $p < 0.05$ were considered significant; data are expressed as mean $\pm$ SD.

Unlike Mountakakis [5], but in agreement with Kister et al. [6], we found no significant difference between plasma or erythrocyte magnesium values of the healthy subjects and those of patients on regular hemodialysis, whereas rHuEPO administration triggered at time 90 min a reduction of erythrocyte magnesium in the hemodialyzed patients but not in the healthy controls (table 1).

Our data seem to rule out that erythropoietin might cause an important modification in the quantity of magnesium in healthy subjects. However, the ion appears to behave differently in patients with chronic renal failure, in whom it causes a reduction in the erythrocyte magnesium.

Among the factors that could explain the different effects the hormone has in the two groups of subjects, is the different calcium content found in uremic subjects [7], the increase in magnesium concentrations in the cell membranes of such patients [6], and, above all, the different activities of a number of ionic pumps, also because of the presence of substances with an inhibitory effect [8].

In conclusion, in uremic patients who routinely receive replacement erythropoietin, rHuEPO administration alters the behaviour of magnesium. Further studies evaluating free magnesium and the urinary excretion of the ion after the administration of rHuEPO are required, as they will enable a better clarification on the real impact of erythropoietin on magnesium metabolism in patients on hemodialysis for renal failure.

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