ERYTHROPOIETIN IN THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ANEMIA

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SUMMARY

Diabetes mellitus frequently leads to end-stage renal disease. Diabetic nephropathy develops in approximately 20% of patients with type 1 or type 2 diabetes mellitus after 20 years of diabetes mellitus duration. The correlation between anemia and chronic renal failure caused by diabetes mellitus has been well documented. Erythropoietin is most frequently used in patients receiving dialysis. The initial dose of intravenously administered erythropoietin for adults is 100-180 IU/kg body weight weekly, divided into 3 doses over the week. Hemoglobin (Hgb) and hematocrit (Htc) values should be measured at baseline and then every 2 weeks of treatment introduction as well as after any dose increment or reduction until the target and stable Hgb value is achieved and the erythropoietin maintenance dose determined. Subsequently, Hgb and Htc values should be determined every 4 weeks. All patients receive erythropoietin intravenously in doses from 2000 to 12000 IU weekly. Not all patients with chronic renal failure should be treated with erythropoietin, as 20% of patients on hemodialysis and 40% of those on peritoneal dialysis can maintain Hgb concentrations above 100 g/L and Htc above 0.30 with appropriate dialysis and dietary regimen and adequate iron stores. In patients receiving peritoneal dialysis it is not necessary to introduce erythropoietin therapy during the first 3 months of dialysis, because elevated Hgb concentrations (mean 10-20 g/L) can be expected in this initial period. Patients with chronic renal failure should have an adequate iron concentration (0.33) to achieve and maintain Hgb concentration at a minimum of 110 g/L. Erythropoietin can be administered subcutaneously, intravenously or intraperitoneally into ‘dry abdomen’, which should be left so for 6-8 hours. On intraperitoneal erythropoietin administration higher doses are required (by 15%-50%) than when it is administered subcutaneously or intravenously. Clinical usage of erythropoietin has not been defined in patients with type 2 diabetes mellitus and renal damage with anemia who have not yet developed end-stage renal disease.

Erythropoietin is a glycoprotein hormone that is mainly secreted by tissue cells in the interstitial peritubular areas of the renal cortex in adults. Erythropoietin secreting cells are specialized fibroblasts and/or endothelial cells of peritubular capillaries. A considerably lower erythropoietin level is synthesized in hepatocytes, macrophages and liver Kupffer’s cells. The main and basic erythropoietin function is to stimulate erythropoiesis, that is, erythropoietin is the main erythropoiesis regulator provided the iron concentration in the body is sufficient. The main erythropoietin secretion signal is the hypoxic state of the tissue, where erythropoietin producing and secreting cells are found. The increased erythropoietic activity is evident in intensified erythropoiesis, which leads to depletion of body iron stores. Hypoxia reduction and elimination lead to
reduced erythropoietin production (1). Erythropoietin affects erythropoiesis cells by a specific erythropoietic receptor (EPO-R), which is for its structural characteristics and intracellular signal transmission classified in the group of cytokine receptors, i.e. receptors for hematopoietic cytokines (2). Erythropoietin binding results in receptor dimerization, i.e. binding of two single-layer receptor channels. Dimerization is the basic precondition for receptor activation and signal transmission to the cell. Erythropoietic receptors are found exclusively in the erythrocyte line cells, and this only in some developing forms. For the time being, it is considered that there are at least two binding EPO-R sites of different affinities for erythropoietin. The presence of endogenous factor that increases affinity for erythropoietin has also been confirmed (3). Erythropoietin is most frequently used in patients receiving dialysis. The initial dose of intravenously administered erythropoietin for adults is 100-180 IU/kg body weight weekly, split into 3 doses over the week. Higher initial erythropoietin doses can be administered in patients with complex illnesses that have caused anemia or pernicious anemia. Hemoglobin (Hgb) and hematocrit (Htc) should be measured at baseline, and then every 2 weeks of the treatment initiation as well as after any dose increment or reduction until the target and stable Hgb value is achieved and maintenance dose of erythropoietin determined. Subsequently, Hgb and Htc values should be determined every 4 weeks. Side effects of erythropoietin therapy may include hypertension, convulsions, hyperkalemia (observed in some previous studies but not in recent ones), and vascular thrombosis. The procedure of preserving aortocaval fistula (AC) or vascular implant from developing thrombosis (since Htc exceeding 0.33 is known to increase the incidence of coagulation) has not yet been determined.

Erythropoietin therapy achieves the main aims of anemia management:

- reduced need of blood transfusions,
- anemia symptoms are eliminated and the patient quality of life is greatly improved;
- the sequels of anemia on the cardiovascular system, brain and endocrine functions are reduced, and
- side effects of the treatment for anemia are decreased.

The prevalence of diabetes mellitus continues to increase in the world, and it is expected to be 32,000,000 diagnosed diabetic patients in Europe in 2010. Diabetes mellitus frequently leads to end-stage renal disease. Diabetic nephropathy develops in approximately 20% of patients with type 1 or type 2 diabetes mellitus after 20 years of diabetes mellitus duration. The correlation between anemia and chronic renal failure due to diabetes mellitus has long been known. The pathophysiologic processes of anemia development begin much earlier than the first demonstrable clinical signs of uremia. A great number of scientific findings and clinical studies suggest that anemia in diabetic patients had developed much earlier than the clinical and laboratory parameters of renal damage were identified (4-7).

Clinical efficacy of erythropoietin was investigated in several uncontrolled clinical studies including a considerable number of adult patients with diabetes. Open clinical trials were the following: European multicenter study, Brasillian multicenter study, Argentinian multicenter study, and three Indian studies in a total of 946 patients (8-11). These studies demonstrated with certainty that erythropoietin influenced erythropoiesis stimulation. The efficacy of erythropoietin was evaluated by the increase in Htc, Hgb and reticulocyte concentrations and patient general health improvement, i.e. psychophysical condition. The latter was determined by ergometric tests, patient subjective assessment of his/her health condition, and brain functions. The treatment for the causes of anemia in chronic renal failure should be introduced when the concentration of Hgb is lower than 110 g/L and of Htc lower than 0.33 in prepubertal patients and premenopausal women. In postmenopausal women the treatment of anemia should be initiated when the concentration of Hgb is lower than 120 g/l and of Htc lower than 0.37 (12,13).

Data from the registry of the Croatian Documentation and Reference Center for Transplantation show that since May 2003, 2562 patients have been included in the chronic renal failure treatment program receiving extracorporeal hemodialysis in 38 centers for dialysis, whereas 2562 patients have been waiting for transplantation. All patients receive erythropoietin intravenously in doses from 2000 to 12000 IU weekly. The mean weekly erythropoietin dose is approximately 8000 IU. In the Republic of Croatia, 222 patients are
treated by peritoneal dialysis, and 10% of them receive erythropoietin for the treatment of anemia. The mean weekly erythropoietin dose is approximately 4000 IU (14).

At the Vuk Vrhovac University Clinic, 25 patients with diabetes mellitus have been treated by extracorporeal hemodialysis, whereas two patients receive peritoneal dialysis. Some 90% of these patients are treated with erythropoietin. The mean weekly erythropoietin dose is approximately 8000 IU. At the Vuk Vrhovac University Clinic Outpatient Department of Nephrology, 682 patients with nephropathy manifested by azotemia, microalbuminuria or proteinuria are being treated. In 80 (11.73%) patients, Hgb is lower than 110 g/L, Htc is lower than 0.33, and creatinine is higher than 125 µmol/l.

Not all patients with chronic renal failure should be treated with erythropoietin, as 20% of patients on hemodialysis and 40% of those on peritoneal dialysis can maintain Hgb concentration above 100 g/L and Htc above 0.30 with appropriate dialysis and dietary regimen and adequate iron stores. Erythropoietin therapy should be introduced if Hgb level is continuously below 110 g/L, and Htc concentration is lower than 0.33, and if other causes of anemia have been ruled out. In patients on peritoneal dialysis it is not necessary to introduce erythropoietin therapy during the first 3 months of dialysis therapy because an elevated Hgb concentration (mean 10-20 g/L) can be expected during this initial period (12,13). Patients with chronic renal failure should have an iron concentration that is adequate to achieve and maintain an Hgb concentration of at least 110 g/L, i.e. Htc concentration of 0.33. To achieve and maintain these values, patients should receive a sufficient amount of iron, which can be determined from serum iron and ferritin levels that should be higher than 100 mg/L, i.e. hypochromic erythrocytes lower than 10% (TSAT higher than 20%). In nondialyzed patients with chronic renal failure and in patients receiving hemodialysis or peritoneal dialysis, erythropoietin can be administered subcutaneously, intravenously or intraperitoneally into 'dry abdomen', which should be left so for 6-8 hours. Intraperitoneal erythropoietin administration requires higher doses (by 15%-50%) than subcutaneous or intravenous route of administration (15).

The clinical usage of erythropoietin has not yet been defined for patients with type 2 diabetes mellitus and renal damage with anemia, who have not yet developed end-stage renal disease. Neither has the possible benefit of early erythropoietin intervention for the patient quality of life and delayed development of cardiovascular complications and death been objectively determined. Additional clinical studies are needed that might provide further objective evidence for possible early erythropoietin intervention rationality and benefit in this patient group.

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