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CLINICAL PHARMACOLOGICAL APPROACH TO DRUGS USED IN THE TREATMENT OF THROMBOEMBOLIC SYNDROME IN THE ELDERLY

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ABSTRACT

Anemia and venous thromboembolic complications are conditions that are not specific to any one nosology. Today, erythropoiesis-stimulating drugs are widely used to correct anemia. However, an increase in hemoglobin/hematocrit is not unambiguously positive, since it can potentially increase the tendency to thrombosis in the venous bed. This tendency is expressed differently in different diseases and conditions. Opinions on erythropoiesis-stimulating drugs as real risk factors for the development of venous thromboembolic complications also differ.

Keywords: Anemia, thrombosis, hemoglobin, erythropoiesis-stimulating drugs, blood viscosity, costs.

INTRODUCTION

Medicines that stimulate erythropoiesis have found wide application in practice. This is due to the fact that anemia is a condition that is not specific to any one nosology. It can be congenital, caused by various reasons by insufficiency of the red germ and/or erythropoietin production, or develop against the background of a particular disease and/or condition associated with suppression of erythropoiesis, erythropoietin deficiency, blood loss, or, for example, a combination of these reasons. The amount of oxygen delivered to organs depends on three factors: blood flow and its distribution, hemoglobin concentration, and oxygen extraction in tissues. Anemia is compensated by non-hemodynamic and hemodynamic reactions: the former are increased production of erythropoietin to stimulate erythropoiesis and increased oxygen extraction. Increased cardiac performance is the main hemodynamic factor mediated by a decrease in afterload, an increase in preload, and positive inotropic and chronotropic effects. In addition, anemia increases the heart rate due to the stimulating effect of hypoxia on chemoreceptors and an increase in sympathetic activity. However, in the long term, these hemodynamic changes lead to the gradual development of dilated cardiomyopathy with left ventricular hypertrophy.

MATERIALS AND METHODS

Erythropoietin is the main regulator of erythropoiesis. It stimulates the formation of erythrocytes from late progenitor cells and increases the yield of reticulocytes from the bone marrow. The glycoprotein hormone erythropoietin is produced mainly by the kidneys in adults. A small amount of erythropoietin is synthesized in the liver. The production of erythropoietin depends on the relationship between tissue oxygen requirements and its supply: the kidneys and liver secrete erythropoietin in response to hypoxia. Erythropoietin promotes the proliferation and differentiation of erythroid cells and prevents their apoptosis. To perform the latter function, the concentration of erythropoietin must be maintained at a certain level,

constant for each person. As long as tissue oxygenation is not impaired, the concentration of erythropoietin, as well as the volume of circulating red blood cells, remains constant.
Erythropoietin is an extremely active hormone (it exerts its effect in picomolar concentrations), small fluctuations in its concentration in the blood lead to significant changes in the rate of erythropoiesis, and the normal range of its concentrations is quite wide (4–26 IU/L). Therefore, until the hemoglobin concentration falls below 105 g/L, the concentration of erythropoietin does not go beyond the specified range and it is impossible to detect its increase (unless its initial values are known). As the hemoglobin level decreases further, the production of erythropoietin increases exponentially [1]. Therefore, it is natural that today the most frequently used erythropoiesis-stimulating drugs (ESD) include the recombinant drug epoetin alpha, a glycoprotein that specifically stimulates erythropoiesis, activating mitosis and the maturation of erythrocytes from erythrocyte precursor cells.

RESULTS AND DISCUSSION

Recombinant technology of its production allowed to achieve that in its composition, biological and immunological properties epoetin alpha is practically identical to natural human erythropoietin. As a result, the introduction of this drug leads to an increase in the concentration of hemoglobin and the value of hematocrit, which naturally contributes to the improvement of tissue blood supply. Therefore, the main indications for the use of ESP are:

- anemia caused by erythropoietin deficiency (for example, in patients with chronic renal failure - CRF);
- anemia associated with oncological diseases and ongoing chemo- and radiotherapy;
- anemia caused by immune (autoimmune) processes;
- anemia as a result of massive blood loss due to surgery, trauma, etc.;
- anemia of pregnant women.

It is worth noting that the appointment of ESP is quite attractive for those conditions that may be accompanied by hypoxic complications. However, considering this list, it should be noted that the same conditions and diseases are characterized by an increased risk of developing deep vein thrombosis (DVT) and thromboembolism in the pulmonary artery basin (PE), i.e. venous thromboembolic complications (VTEC). VTEC ranks 3rd in terms of frequency of development after coronary heart disease and stroke [2]. The main risk factors for the development of VTEC include extensive trauma and surgery, cancer and chemotherapy, nephrotic syndrome, varicose veins, age over 40, pregnancy and the postpartum period, metabolic and immune disorders, long-term venous catheterization, cardiovascular diseases, and a number of other factors [3]. The incidence and side effects of ESP vary according to different authors. Several studies have recently highlighted the problem of an increased tendency for tumor progression, increased mortality, and the incidence of VTEC. It is also certain that the biological background underlying the prothrombotic effects of ESP is very multifaceted (polycythemia/hyperviscosity syndrome, hypertension, thrombocytosis, platelet hyperactivity, activation of blood coagulation). This, in turn, does not allow us to unequivocally assess ESP therapy as beneficial or not for patients with anemia. Therefore, according to G. Lippi et al. (2010), such drugs should not be routinely used as an alternative to blood transfusion until future studies confirm (or refute) their clinical benefit [4]. In this regard, it

is advisable to consider the problem of the development of VTEC against the background of ESP intake for various diseases and conditions.

Analyzing this study, two facts should be noted:

1) the obvious inadequacy of the selection of the antithrombotic prophylaxis regimen, since VTEC (total DVT and PE) developed in 14% of patients;

2) the prophylactic administration of erythropoietin to patients with hemoglobin above 120 g/l (i.e. the hematocrit value was at least 38%).

In the latter case, the question arises about the advisability of prescribing erythropoietin. On the one hand, the maximum oxygen capacity of the blood is achieved already at a hematocrit value of 27–29%, i.e. with a hemoglobin content of 90–95 g/l. Such values of hematocrit and hemoglobin are considered as triggers: detection of lower values in a patient can already be assessed as anemia and suggest the use of specific means of its correction (blood transfusions, ESP, iron-containing drugs, etc., depending on the causes and type of anemia). On the other hand, it is in patients (and not healthy people!) with a hematocrit over 36–39% that the procoagulant tendency begins to prevail and the viscosity of whole blood increases, which is largely the result of hemoconcentration [10]. The consequence is a sharp increase in the risk of developing VTEC. Somewhat later, in 2006, similar data were obtained that the hemoglobin level, upon reaching which treatment with ESP can be stopped, is associated with the relative risk of developing VTEC [3]. As can be seen, the risk of developing VTEC in cancer patients increases sharply (up to 1.71) already at a hemoglobin concentration of 130–140 g/l (approximate hematocrit value of 41–44%) and continues to increase with an increase in hemoglobin concentration, reaching the highest values at a hematocrit of more than 48–50%. Therefore, the appointment of ESP for cancer diseases requires a mandatory assessment of their feasibility in a specific clinical situation: an assessment of the "benefit (correction of anemic condition and hypoxia) / risks (development of VTEC)" ratio.

Progressive renal failure is almost always accompanied by moderate or severe hyporegenerative anemia, and the increase in renal failure is usually accompanied by an increase in anemia. When blood urea nitrogen reaches 36 mmol / l, and the serum creatinine concentration exceeds 265-442 μmol / l, the hemoglobin concentration falls below 70 g / l. This is due to two reasons at once: a sharp shortening of the lifespan of erythrocytes against the background of uremia and a decrease in the production of erythropoietin due to kidney damage [2]. Renal dysfunction is also characterized by the simultaneous presence of tendencies to hemorrhagic diathesis and hypercoagulation. The tendency to hypocoagulation increases with the progression of CRF due to increased uremia. However, such hypocoagulation is reversible with adequate therapy of CRF and correction of concomitant anemia using ESP. In contrast, a tendency toward hypercoagulation is usually encountered in patients with nephrotic syndrome in combination with severe hypoalbuminemia (<20 g/l) and critically impaired fibrinolysis [3]. Therefore, an increase in hemoglobin concentration due to the use of ESP in patients with CRF raises the question of the risk of developing VTEC in them. A. Christensson et al. [4] studied changes in hemostatic parameters after 3 and 12 months of continuous ESP intake to achieve a subnormal hemoglobin level in patients with terminal CRF. Of the entire fairly large range of hemostatic parameters, reliable changes (a decrease demonstrating a prothrombotic tendency) were noted only for protein S activity after 3 months of ESP therapy.

And after 12 months, such differences were no longer detected. On this basis, the authors conclude that there is no prothrombotic tendency in patients with CRF after normalization of hemoglobin levels with drugs that stimulate erythropoiesis [4].

CONCLUSION

Today, the modern pharmaceutical industry, both foreign and domestic, offers a wide range of medicines. If we do not mean counterfeit products, then in the vast majority of cases the drugs produced are well purified and have high efficiency. Therefore, in the event of the development of side effects, complications, etc. against the background of the use of a particular drug, the opinion that the drug is "bad" is fundamentally wrong. I would not like to offend anyone, but in the vast majority of such cases, it is the doctor who turns out to be "bad", who was not sufficiently informed and prepared to work with the drug.

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