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POSSIBILITIES OF CORRECTION OF IRON DEFICIENCY ANEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Summary. *The effectiveness of intravenous infusion of iron sucrose (Sufer®) for 2 weeks in 12 patients with iron deficiency anemia, caused by chronic kidney disease, who were examined and treated in Nephrology department of Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov, was evaluated. Treatment with the iron (III) hydroxide sucrose complex resulted in a significant increase of plasma hemoglobin, ferritin and iron levels, contributed to a decrease in creatinine level (p<0.01). Increase of hemoglobin level was started at a 5-day treatment. After 2 weeks hemoglobin level increased by 13% (p<0.01). There were no significant side effects, that would be require changing the daily dose of the drug or discontinuation of treatment. The therapeutic effect and good tolerability of iron (III) hydroxide sucrose complex allow to recommend it as a drug of choice for iron deficiency anemia in patients with chronic kidney disease.*
Key words: *chronic kidney disease, iron deficiency anemia, iron sucrose, Sufer®.*

Introduction

Anemia is the earliest and the most frequent complication of chronic kidney disease (CKD) and usually develops with a decrease in glomerular filtration rate (GFR) to 40-60 ml/min/1.73 m^2, although it is possible in the early stages of kidney disease. Anemia is detected in approximately half of the patients with CKD (Astor B.C. et al, 2002; V.M. Ermolenko, N.N. Filatova, 2004). The prevalence and severity of anemia in Ukraine is considerably higher than the similar indicators in developed countries. Thus, according to European Survey of Anaemia Management – ESAM, in Western Europe 53% of patients with CKD achieve the target level of hemoglobin > 110 g/l, in Ukraine – not more than 20%, according to the data of the CKD patients register (L.Yu. Milovanova and co-authors, 2009). In addition, a large number of patients is registered with critically low hemoglobin level - <70, and even <60 g / l (Astor B.C. et al, 2002).

Anemia develops especially due to the loss of kidney's ability to secrete sufficient amount of erythropoietin to stimulate haematopoiesis. Anemia in CKD may occur long before the terminal stage and may be aggravated with its progression, as renal scarring leads to decrease in the synthesis of erythropoietin in peritubular cells. Other causes of anemia in patients with CKD — shortening of life of red blood cells, platelet dysfunction, causing increased bleeding, impact of uremic toxins on red blood cells, reduction of iron content due to inadequate absorption in the intestine and in hemodialysis, removal of folic acid with hemodialysis, osteofibrosis induced by parathyroid hormone. Typical for healthy individuals inverse linear dependence between the level of erythropoietin in blood plasma and hemoglobin concentration is disturbed in development of renal failure. As a result, the synthesis of erythropoietin is not increased in proportion to the severity of anemia (Hsu C.Y. et al., 2002; Hörl W.H. et al., 2003; Locatelli F. et al., 2004; V.V. Berezhna and co-authors, 2006; E.V. Karmanov, 2010).

Anemia increases the risk of undesirable outcomes in patients with CKD, such as mortality, the progression of CKD and cardiovascular diseases, hospitalization. The issue of anemia correction is relevant to the patients on pre-dialysis and dialysis stages of CKD and after kidney transplantation.

In recent years, particular attention is paid to the correction of anemia in patients with early stages of CKD. It is established that the early, on pre-dialysis stages of CKD, correction of anaemia with erythropoietin and iron preparations improves quality of life and reduces the risk of death from cardiovascular complications in CKD patients during the subsequent program dialysis (G.V. Volgina and co-authors, 2000; The National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2000; L.Yu. Milanova and co-authors, 2009; E.V. Karmanov, 2010). Therefore, correction of anemia can be considered as an important part of the strategy to reduce the risk of morbidity and mortality of patients with CKD, both before and after the start of dialysis.

We should not forget about the need for correction of iron deficiency anemia in patients with chronic renal failure (CRF). Iron deficiency develops with the progression of uremia due to malabsorption of iron in the gastrointestinal tract, blood loss or increased iron consumption for the needs of erythropoiesis in the treatment with epoetin preparations (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2000). Iron in the heme structural unit of haemoglobin provides binding, transportation and transfer of oxygen to tissues and in conjunction with chromoproteids of tissues takes part in the process of biological oxidation (Locatelli F. et al., 2004).

Correction of anemia in patients with CKD stages III-V is based on combined use of epoetin and iron preparations, acting synergistically (Locatelli F. et al., 2004; Dobronravov V.A., Smirnov A.V., 2005). The iron content in the body should match the level of erythropoietin for full implementation of proliferative possibilities of an erythroid lineage. If intake of iron in the bone marrow is insufficient then production of red blood cells is reduced, and with a deep iron deficiency haemoglobin synthesis is disturbed and iron-deficient hematopoiesis develops (Locatelli F. et al., 2004; V.A. Dobronravov, A.V. Smirnov, 2005). Note that epoetin preparations stimulate the synthesis of about 2 million new red blood cells per 1 sec (E.V. Karmanov, 2010). With a lack of available iron reticulocytes with low hemoglobin content come from the bone marrow into the blood (Cody J. et al., 2005; E.V. Karmanov, 2010). Despite the variation in hemoglobin levels in patients with CKD, a significant decrease is (<110 g/l) naturally noted for severe stage of renal failure;

GFR <30 ml/min/1.73 m^2. In its turn, an adequate amount of available iron stimulates erythropoiesis and reduces the need for epoetin (E.V. Karmanov, 2010).

A higher efficiency of intravenously administered iron preparations in comparison with oral drugs is confirmed (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2000). At the same time, data of randomized study J. Stoves et al (2001) showed no differences between the intravenous (iron sucrose at a dose of 300 mg/month), and oral (ferrous sulfate at a dose of 600 mg/day) administration of iron preparations in progressive renal failure patients. In patients with uremia intestinal absorption can be maintained at the level necessary for compensation of daily loss of iron from the gastrointestinal tract and with blood sampling for laboratory tests.

Therefore, intravenous administration of iron in patients with CKD, especially in patients receiving hemodialysis and/or epoetin, is more effective than oral administration of iron preparations. However, from a practical point of view, the possibility of oral administration of iron preparations is not excluded in patients with CKD in predialysis stage.

Methods, doses and frequency of administration of epoetin preparations for the treatment of anemia in patients with CKD in different stages are defined by American and European recommendations (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2000; Locatelli F. et al., 2004), in relation to iron preparations in predialysis stages of CKD uniform regulations are absent. Note that these guidelines are actively discussing the use of parenteral forms of iron preparations based on dextran. However, unlike the last one, the use of iron sucrose is associated with good tolerability, as confirmed in a study conducted on the basis of 61 sites in US: on the background of administration of 8590 doses of iron sucrose in 665 patients on hemodialysis, side effects were not observed (Yee J., Besarab A., 2002). In this regard, the possibility of using iron sucrose in higher doses in patients with CKD and discontinuation of iron in form of low molecular weight dextran as first line treatment in patients with anemia in renal disease is considered.

Thus, the problem of anemia correction, discussions in regard to different therapeutic approaches is one of the most frequent discussion topics within specialized medical, including nephrology, forums. However, almost for the first time, we are discussing the role and place of iron preparations, differentiated strategies for their use in patients with CKD in the extended format. First of all, this is due to global tendencies, clearly displayed in the practical clinical recommendations of KDIGO (2013) for anemia in CKD. In this guidance compared with previously known, the target hemoglobin level is reduced, the tendency to reduce the use of erythropoietin in ultra-high doses is noted, wider use of iron preparations is recommended, attention on the careful use of erythropoiesis-stimulating agents in patients with CKD and active malignant tumors, history of stroke or cancer pathology is focused.

Today the strategy of intravenous administration of iron preparations depends on the availability of specific preparations in different countries. In Ukraine, according to the State Register of Medicinal Products, iron sucrose for intravenous use Sufer® (Yuria-Pharm) is registered and permitted for use.

The aim of our study is to assess the efficacy of intravenous iron preparation Sufer® in patients with iron deficiency anemia, associated with CKD.

Study object and methods

12 patients with chronic renal failure were examined, including 7 (58.3%) women and 5 41.7%) men; mean age – 52.25 ± 8.80 years. The patients were examined and treated in the Nephrology Department of Dnepropetrovsk Regional Clinical Hospital named after I.I. Mechnikov. The causes of CRF were chronic pyelonephritis (25%), chronic glomerulonephritis (41.7%) and diabetes mellitus (33.3%).

The examination included the determination of hemoglobin, iron, ferritin levels in blood plasma, characteristics of clinical anemia symptoms.

Diagnosis of anemia was confirmed on the basis of criteria proposed in the recommendations of The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (2000), according to which the anemia of chronic renal failure is diagnosed at hemoglobin level <110 g/l.

For clinical assessment of renal function creatinine level was determined in blood plasma using colorimetric methods, and GFR was calculated using the formula by D.W. Cockcroft, M.H. Gault (1976).

Criteria for inclusion in the study: the presence of CKD stage I-III, iron deficiency anemia, hemoglobin level <110 g/l, GFR 30-89 ml/min/1.73 m^2, absence of erythropoietin preparations administration, patient's consent.

Criteria for exclusion from the study: anemia of different origin, associated with acute blood loss, hypothyroidism, malabsorption syndrome, patient's refusal.

For the purpose of anaemia correction Sufer® was administered to patients in the form of a solution for parenteral administration, 1 ml of which contains 20 mg of iron as iron (III) hydroxide sucrose complex.

Dose was calculated individually according to the general iron deficiency in the patient using the formula:

total iron deficiency (mg) = body weight (kg) (normal hemoglobin (g/l) - level of the patient's hemoglobin (g/l)) + 0.24 level of deposited iron (mg).

If the total required dose exceeded the maximum allowed single dose, the drug was injected in parts. The observation period was 2 weeks.

Clinical effect was evaluated after the end of observation period with reduction of the severity of clinical manifestations of anemia, complaints from the patient, as well as data of laboratory examination. Clinical effect was determined according to the following criteria: high efficiency (normalization of laboratory blood parameters, the absence of clinical manifestations of anemia); moderate efficacy (a statistically significant improvement of laboratory blood parameters, reduction of the severity of the clinical manifestations of anemia), low efficiency (no statistically significant changes in blood parameters, a slight decrease in the severity of clinical manifestations of anaemia).

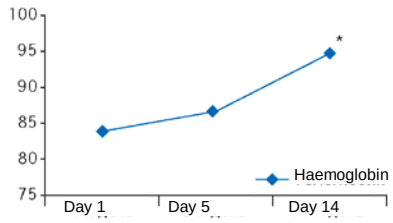
Safety of the preparation was studied on the dynamics of biochemical blood parameters (total protein, alanine aminotransferase (ALT), aspartat aminotransferase (AST), alkaline phosphatase, bilirubin, creatinine, urea), and urinalysis.

Statistical processing of the data was performed using STATISTICA 6.1 program (StatSoft Inc., USA). Mean values (M), standard deviation (SD), standard error of mean value (m) were determined. Mann-Whitney U-test and Wilcoxon test (W) were used to compare parameters in two independent groups. The assessment of the relationship between pairs of independent features, expressed in a quantitative scale, was performed using the Spearman's rank correlation coefficient (r). Statistically significant differences in results were determined at $p < 0.05$.

Study results and their discussion

Symptoms of anemia among the study patients were different and significantly worsened their health. The most common symptoms of anemia were: fatigue (66.7% of patients), weakness (66.7% of patients), headache (83.3% of patients), dizziness (66.7% of patients), decreased appetite (58.3% of patients), palpitation (16.7% of patients), dyspnea (8.3% of patients). After 2 weeks of treatment with the preparation improvement of health, reduction of clinical manifestations of anemia were observed in the majority of patients (Table 1).

Figure



Dynamics of hemoglobin levels during the treatment with preparation Sufer® in patients with CKD

Significance of differences of parameters before and after treatment, p <0.01.

When analysing the initial data reduced levels of hemoglobin, erythrocytes and iron in blood plasma were revealed. It should be noted that none of the examined patients received therapy with epoetin.

Depending on the hemoglobin level patients were divided into two groups: group 1 (n=4) – patients with hemoglobin level of 90-110 g/l, group 2 (n=8) – 70-90 g/l (Table 2). No significant differences were found between the groups.

Inclusion of iron (III) hydroxide sucrose complex in the therapy resulted in a significant increase in hemoglobin, ferritin and iron levels in the blood plasma (p <0.01). It should be noted that in the end of observation a significant increase in the level of red blood cells was found only in group 2 (p <0.01) (Table 3). At the same time after 2 weeks of observation the level of hemoglobin in the group 1 was increased by 10.5%, in the group 2 – by 14.5%, respectively (p <0.01).

During the period of observation no statistically significant dynamics of blood pressure and heart rate was identified.

To evaluate the effect of preparation, patients were divided into two groups depending on the level of ferritin: group 1 (n = 7) – patients with ferritin level <100 ng/ml, group 2 (n = 5) – 100-200 ng/ml. After 2 weeks on the background of treatment a significant increase in hemoglobin, ferritin and iron levels was revealed (p <0.01) (Table 4).

Analysis of the relationship between the parameters shows a direct correlation between the levels of ferritin and hemoglobin in group 1 (r = 0.50; p <0.05), and in group 2 (r = 0.20; p <0.05). In this case the relationship between the levels of ferritin and iron was found only in group 2 (r = 0.44; p <0.05).

During the period of observation it was established that among the examined patients an increase in hemoglobin level started from the 5th day of treatment (Figure). Hemoglobin level increased by 13% (p <0.01) after 2 weeks.

Creatinine was measured and GFR was calculated in patients to assess kidney function on the background of anemia (Table 5). After the observation no significant changes in GFR among study participants were noted, however, a significant decrease in creatinine level was found in both groups (p <0.01).

Table 1 Change of clinical manifestations of anemia on the background of treatment (n=12), n (%)

Symptom	Before treatment	After treatment
Increased fatigue	8 (66.7)	3 (25.0)
Weakness	8 (66.7)	2 (16.7)
Headache	10 (83.3)	-
Dizziness	8 (66.7)	2 (16.7)
Decreased appetite	8 (66.7)	-
Palpitation	2 (16.7)	-
Dyspnea	1 (8.3)	-

Table 2 Characteristics of parameters, depending on the hemoglobin level

Parameter	Group 1 (n=4)	Group 2 (n=8)
Age, years	52.00+9.52	52.37+9.10
Body weight, kg	82.00±1.63	73.87±8.09
Body mass index, kg/m^2	28.42±1.74	26.01±2.86
Red blood cells, × 10^{12}/ l	2.70±0.59	2.54±0.51
Hemoglobin, g/l	97.25±4.99	77.25±6.25
Ferritin, ng/ml	161.37±40.83	128.98±13.71
Iron, μmol/l	6.74±1.75	5.18±3.65
Systolic blood pressure (BP), mmHg.	145.00±20.41	155.00±25.63
Diastolic BP, mmHg.	86.25±10.30	91.62±12.29
Heart rate (HR), beats per minute	72.00±3.26	75.62±6.92

Table 3 Dynamics of parameters with treatment

Parameter	Before treatment		After treatment	
	Group 1	Group 2	Group 1	Group 2
Red blood cells, × 10^{12}/l	2.70±0.59	2.54+0.51	3.16+0.57	2.93±0.47*
Hemoglobin, g/l	97.25±4.99	77.25±6.25	107.50±5.25*	88.50±7.07*f
Ferritin, ng/ml	161.37±40.83	253.98±84.65	439.95±58.59*	357.66±53.74*
Iron, μmol/l	6.74±1.75	8.18±3.65	14.30±2.35*	20.28±9.64*
Systolic BP, mmHg.	145.00±20.41	155.00±25.63	141.25±19.73	149.37±20.07
Diastolic BP, mmHg.	86.25±10.30	91.62±12.29	82.50±6.45	87.50±8.86
HR, beats per minute	72.00±3.26	75.62±6.92	70.00±1.63	72.50±5.70

*In table 3-5: significance of differences in parameters before and after treatment (p <0.01); Significance of differences in parameters between groups after treatment (p <0.05).

Table 4 Dynamics of parameters with treatment depending on the ferritin level

Parameter	Group 1 (n=7)		Group 2 (n=5)	
	Initial condition	At the end of the observation	Initial condition	At the end of the observation
Red blood cells, × 10^{12}/l	2.59+0.51	3.03+0.41*	2.60+0.59	2.97±0.64*
Hemoglobin, g/l	85.00±11.43	96.14±11.75*	82.40±12.36	93.00±11.59*
Ferritin, ng/ml	61.70±12.92	312.90±71.16*	149.10±11.11	509.36±19.80*
Iron, μmol/l	6.66±2.57	16.24±6.88*	9.15±3.54	21.15±10.09*

Table 5 Dynamics of parameters with treatment depending on the hemoglobin level

Parameter	Group 1		Group 2	
	Initial condition	At the end of the observation	Initial condition	At the end of the observation
Creatinine, μmol/l	318.25+99.8	272.00+93.47*	311.00+20.24	273.25+28.84*
GFR, ml/min/1.73 m^2	38.43±7.26	42.23±3.54	36.77±14.48	40.34±4.58

Table 6 Dynamics of ALT, AST and bilirubin levels before and after treatment

Parameter	Group 1		Group 2	
	Initial condition	At the end of the observation	Initial condition	At the end of the observation
ALT, U/l	18.50±0.85	20.00+0.87	18.70+0.81	19.70+0.78
AST, U/l	21.70±0.87	23.00±0.98	22.00±0.90	22.00±0.85
Bilirubin, μmol/l	13.70±0.34	14.20±0.27	13.90±0.18	14.50+0.22

No significant side effects were revealed in the use of preparation. At the end of the observation compared with the initial condition no significant changes in ALT, AST, bilirubin levels were observed, which indicates a good tolerability of therapy (Table 6).

Thus, a good therapeutic effect and tolerability of iron (III) hydroxide sucrose complex allow to recommend it as a drug of choice for iron deficiency anemia in patients with CKD.

Conclusions

1. Parenteral administration of iron (III) hydroxide sucrose complex improves blood parameters (contributes to an increase in plasma red blood cells, hemoglobin, ferritin and iron levels, contributes to a decrease in creatinine level (p<0.01).

2. Iron (III) hydroxide sucrose complex is safe when used in patients with iron deficiency anemia, associated with CKD, it does not cause significant side effects, requiring changes in daily dose or treatment discontinuation.

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