UDC (Universal decimal classification) 616.61+616.155.194.8

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The efficacy and safety of the drug Sufer® in correction of anemia in patients with chronic renal failure

The data of the effectiveness of the drug Sufer® in patients with iron-deficiency anemia due to chronic renal failure were analyzed. *The use od the drug helped to improve both clinical and laboratory parameters. Already in the 2nd week of treatment there was a significant increase in the level of hemoglobin, ferritin and iron in the blood plasma, as well as a decrease in creatinine — the main criterion for assessing the functional capacity of the kidneys. The regression of clinical manifestations of the disease, such as loss of appetite, headache, weakness, fatigue, was observed. The significant side effects, which could cause a correction of the initial dosing or discontinuation of the drug, were not observed during the therapy. High efficacy and safety of Sufer® allow to recommend it as the drug of choice for treatment of iron-deficiency anemia, caused by the chronic renal failure.* **Key words:** *chronic renal failure, iron-deficiency anaemia, Sufer.®.*

Introduction

Loss of ability kidneys to secrete the sufficient amount of erythropoietin (a hormone that stimulates the processes of hematopoiesis) is one of the major causes of the development of anemia. The last one can occur with chronic kidney disease (CKD) long before its terminal stage and become more severe with the disease progression, as kidney shrinkage leads to the abrupt decrease of erythropoietin synthesis in peritubular capillary cells.

The causes of anaemia development in patients with chronical kidney disease also are:

- reduction in the red blood cell lifespan;
- platelet dysfunction, which leads to excessive bleeding;
- effect of the uremic toxins on the erythrocytes;
- reduction of iron content due to inadequate absorption in the intestine and in hemodialysis;
- elimination of folic acid in hemodialysis;
- parathormone-induced osteofibrosis.

The distortion of inverse linear relationship between plasma erythropoietin level and haemoglobin concentration, which is characteristic of healthy people, is typical for chronical renal failure (CRF): erythropoietin synthesis does not increase in proportion to the severity of anemia (Johansen J.L. et al., 2012; KDIGO Anaemia Work Group, 2012).

The correction of this pathology in patients with CRF stage III-V is based on the simultaneous use of epoetin and iron preparations, which act synergistically. For full implementation of proliferative erythroid lineage capabilities it is necessary, that total iron content in body correlates with the erythropoietin level. Insufficient intake of iron to the bone marrow reduces the production of red blood cells, and a deep iron deficiency disturbs the haemoglobin synthesis and develops iron-deficiency anemia (IDA).

Note that epoetin preparations stimulate about 2 mln of new red blood cells per 1 second. With a lack of available iron in the bone marrow reticulocytes with low hemoglobin come into the blood. . Despite the variation of the value of the last mentioned parameter in patients with CRF, its significant reduction (<110 g/L) is naturally marked on the severe stage of the disease, with the glomerular filtration rate <30 ml/min. In its turn, an adequate amount of available iron stimulates erythropoiesis and reduces the need for epoetin (Rozen-Zvi B. et al., 2008; Курята А.В. и соавт., 2014).

Mild anemia can be identified only according to laboratory findings. Clinical symptoms appear with the moderate anemia due to insufficient oxygen supply of tissues and manifest in general weakness, dizziness, headache, increased heart rate, shortness of breath, loss of working capacity and insomnia (Covic A., Mircescu G., 2010).

The iron transport in the blood plasma is associated with its accumulation function in the form of ferritin and hemosiderin (Bailie G.R. et al., 2005). In particular, 65% of the total iron pool is located in hemoglobin, 35% — in myoglobin, 0.5% (a small but functionally important amount) - in tissue enzymes, 0.1% - in blood plasma, and 31% - is in the depot organs (liver, spleen, etc.). A violation of iron deposition in the liver and protein transporters synthesis - transferrin and ferritin occurs in pregnant women with chronic hepatitis and hepatosis, with severe gestosis (Bailie G.R. et al., 2005; KDIGO Anemia Work Group, 2012).

In clinical practice, the major markers, which are often used to identify the iron metabolism pathology are haemoglobin, erythrocyte count, color index and hematocrit. The main criteria of IDA include:

- low color index:
- hypochromic erythrocytes;
- reduced iron level in blood plasma;
- increased total iron binding capacity of blood plasma;
- clinical signs of hyposyderosis.

, The determination of blood plasma ferritin, the content of which, however, does not always reflect the actual reserves of this mineral in the body, is also used to assess the amount of iron, deposited in the body. It also depends on the speed of ferritin release from the tissue and blood plasma (Hörl W.H., 2013; Курята А.В. и соавт., 2014).

There are many preparations for IDA treatment that differ in dosage, dosage form.

Table 1 IDA classification by severity

Severity level	Hemoglobin level, g/l
Mild	110-91
Moderate	90-71
Severe	<70

Table 2 Labaratory parameters of patient's blood before treatment

Parameter	Mean value of the parameter, M±m
Hemoglobin, g/l	82.71+3.15
Erythrocyte sedimentation rate, mm/hr	23.09±4.07
Platelets, • 10*9/l	256.34±11.71
Albumin, g/l	36..33±079
AST, IU/l	0.17±0.02
ALT, IU/l	0.21±0.03
Creatinine, μmol/l	179±1.68
Blood plasma ferritin, ng/ml	138.12±17.31
Ration of transferrin saturation with iron	15.81±1.97

Table 3 Clinical manifestations of anemia in patients before treatment

Clinical manifestations	Number of patients, n (%)
Headache	9 (52.9)
Dizziness	7 (41.2)
Fatigue	13 (76.5)
Appetite loss	11 (64.7)
Shortness of breath	5 (29.4)
Tachycardia	5 (29.4)
Weakness	14 (82.3)

and chemical composition (two- or three-valent iron content). The issue of the benefits of the drugs containing two- or three-valent iron is currently being discussed. The first ones are quite easy and well absorbed by the concentration gradient, but irritate the mucous membrane of the gastrointestinal tract. Patients often complain of heartburn, nausea, heaviness in the epigastric region, metallic taste in mouth, vomiting, defecation disorders. This becomes a reason for their refuse to take the drug (Covic A., Mircescu G., 2010).

Another type of anti-anemic drugs - three-valent iron preparations based on hydroxide-sucrose complex that enters the body more slowly due to more complex mechanisms of absorption, but in contrast to two-valent iron, these drugs have a fewer number of side effects.

The optimal antianemic drug must have high efficiency, convenient dosing schedule, and the negative impact of its use on the quality of life should approach to zero. From this point of view hydroxide-sucrose complex of iron (III) - a drug Sufer® manufactured by ТОВ «Юрія-Фарм» (Ukraine).

The aim of this study is to accesses the efficacy and safety of the obove mentioned drug in the correction of anemia in patients with CKD.

MATERIALS AND METHODS

The study involved 17 patients with CRF: 10 women (58.8%) and 7 men (41.2%), mean age - 57.34 ± 7.7 years. The main causes of CRF: chronic pyelonephritis (47%), CKD (23.5%) and diabetes mellitus (29.4%).

Examination of patients included general clinical examination and laboratory tests with complete blood count and general urine analysis, biochemical analysis with determination of urea, creatinine, total protein, albumin, vitamin B12, folic acid, blood plasma ferritin, ratio of transferrin saturation with iron, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, calcium, phosphorus, parathyroid hormone in the blood. Also, patients' daily urine output was determined and blood pressure monitoring was performed.

The following instrumental techniques were used in the course of the study:

- electrocardiography;
- echocardiography;
- chest X-ray;
- abdominal ultrasound;

Anemia diagnosis in CKD was conducted in accordance with international recommendations on the treatment of acute kidney injury (Kidney Disease Improving Global Outcomes - KDIGO) 2012. The IDA severity was estimated by anemia classification criteria (I.A. Касирського, Г.А. Алексеева (1970) (table 1).

The anemia of different severity was diagnosed according to laboratory findings of blood analysis (table 2), as well as by clinical signs (table 3).

Patients were receiving the drug Sufer® (iron (III) hydroxide-sucrose complex) in the solution for injection 20 mg/ml, 5 ml. The total correction dose was determined according to the manufacturer's recommendations using formula:

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

For people with body weight <35 kg normal hemoglobin level was 130 g/l, the amount of deposited iron - 15 mg/kg; for patients with body weight >35 kg normal hemoglobin level - 150 g/l, the amount of deposited iron - 500 mg.

The coefficient 0.24 = 0.0034 • 0.07 • 1.000 (iron content in hemoglobin is 0.34%, blood volume - 7% of body weight, coefficient 1000: 1 g = 1000 mg).

The drug Sufer® was used at a dose of 200 mg 3 times a week intravenously by drop infusion according to manufacturer's recommendations (the drug was diluted in 0.9% sodium chloride solution and injected into the venous trunk over at least 30 minutes). The duration of treatment was 2-4 weeks, 2.87 ± 0,11 weeks on average.

A test control was performed before the first use of the drug: 20 mg of the drug was administered to the patient over 15 minutes, according to the manufacturer's recommendations. The rest of the dose was administered in the absence of adverse eventsof.

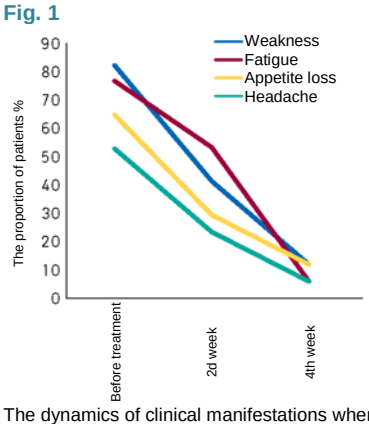
Results and discussion

Improved health and reduced complaints were observed in all patients following the use of iron (III) hydroxide-sucrose complex Sufer® (Fig. 1). In particular, after 2 weeks following treatment initiation only 41.2% of subjects complained about weakness, and after 4 weeks - 11.8%, about the fatigue - 52.9 and 5.9%, about appetite loss - 29.4 and 11.8%, about headache - 23.5 and 5.9%, respectively. The increase in hemoglobin level was marked from 82.71 ± 2.34 to 88.67 ± 4.01 g/l in the 2nd week, to 91.32 ± 3.84 g/L - in the 3rd week and up to 97.84 ± 5.31 g/l - at the end of treatment with the drug Sufer® (Fig. 2). The blood plasma ferritin level increased from 138.12 ± 9.54 to 10.19 ± 253 ng/ml after 2 weeks and up to 417.82 ± 11.08 ng/ml - after 4 weeks of treatment (Fig. 3). A direct correlation between the blood plasmahemoglobin and ferritin levels in patients with CKD was established.

The serum creatinine, which decreased significantly after treatment, was measured to assess renal function in patients: to 131 ± 2.01; 109± 3.01 ± 1.34 μmol/L in the 1st, in the 2nd week and at the end of treatment, respectively (Fig. 4).

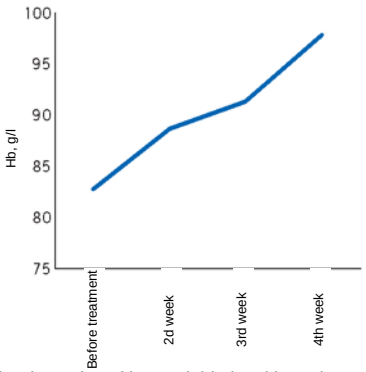
Thus, the parenteral use of iron (III) hydroxide-sucrose complex Sufer® in patients with CRF contributed to the improvement of their general health, normalization of a number of parameters, such as: hemoglobin, blood plasma ferritin and creatinine. The drug showed to be quite safe: There were no significant side effects that would decrease the quality of patients' life.

Fig. 1



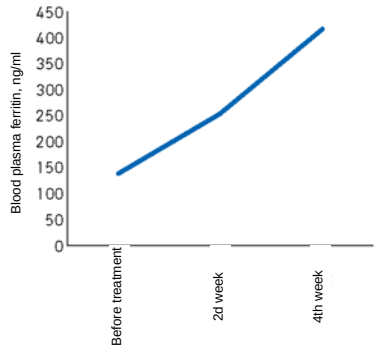
The dynamics of clinical manifestations when using the drug Sufer®

Fig. 2



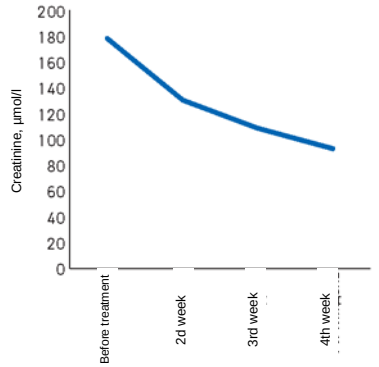
The dynamics of hemoglobin level in patients with chronic renal failure when using the drug Sufer®

Fig. 3



The dynamics of ferritin level in patients with chronic renal failure when using the drug Sufer®

Fig. 4



The dynamics of creatinine level in patients with chronic renal failure when using the drug Sufer®

CONCLUSIONS

1. Iron (III) hydroxide-sucrose complex Sufer® is effective and safe agent for correction of iron deficiency conditions in patients with CKD.
2. The parenteral use of drug Sufer® improves parameters of blood tests: helps to increase the red blood cell amount, hemoglobin, ferritin and iron levels in blood plasma to decrease the creatinine level ($p<0.01$).
3. The drug does not cause significant side effects, that require the daily dose adjustment or discontinuation of the treatment.
4. The correction of iron deficiency requires the monitoring of iron metabolism parameters with subsequent determination of the need to change the dose of the drug to achieve target levels of its characteristics.

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Received on 8.02.2015