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Stimulation of iron-restricted erythropoiesis with iron (III) isomaltoside 1000 does not oversaturate transferrin in haemodialysed patients with anaemia – a retrospective study

Stymulacja za pomocą izomaltozydu 1000 żelaza (III) erytropoezy zahamowanej przez niedobór żelaza u hemodializowanych pacjentów z niedokrwistością nie prowadzi do nadmiernego wysycenia transferyny – badanie retrospektywne

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Słowa kluczowe

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S u m m a r y

Introduction. Iron deficiency, either absolute or relative, contributes to the development of anaemia in end-stage renal failure. Intravenous iron supplementation is a standard treatment in patients on haemodialysis therapy. Available intravenous iron preparations differ in toxicity, dependent on the amount of potentially harmful free iron that is detached from the transporting particle. Interception of free iron by apotransferrin results in TSAT increase.

Aim. The aim of this study was to assess the changes in TSAT after injection of iron (III) isomaltoside 1000 in haemodialysis patients.

Material and methods. The study was conducted in two groups of anemic patients on maintenance haemodialysis for end-stage renal failure. Each group comprised 8 patients with baseline TSAT < 35%. Two weekly doses of 100 mg iron (III) isomaltoside 1000 were administered in the first group. In the second group, 200 mg iron (III) isomaltoside 1000 was administered as the first weekly dose, followed by a 100 mg dose. The changes in TSAT were measured 210 minutes after each administration. The results were analysed with the STATISTICA software.

Results. Both 100 and 200 mg of iron (III) isomaltoside 1000 caused statistically significant, transient increase in TSAT values. TSAT values after 200 mg isomaltoside were significantly higher in comparison to 100 mg ($p = 0.026264$). In neither case the TSAT values reached 60%. No adverse effects of supplementation were observed.

Conclusions. In haemodialysis patients iron (III) isomaltoside 1000 causes moderate and transient increase in TSAT values. The 200 mg iron (III) isomaltoside 1000 seems safe only in patients with significant iron depletion.

S t r e s z c z e n i e

Wstęp. Niedobór żelaza, zarówno względny, jak i bezwzględny, przyczynia się do rozwoju niedokrwistości w przebiegu schyłkowej niewydolności nerek. Dożylna suplementacja żelaza jest standardowym postępowaniem u pacjentów hemodializowanych. Dożylne preparaty żelaza różnią się pod względem toksyczności, w zależności od tego, ile wolnego jonu żelaza, wykazującego szkodliwy wpływ na tkanki, przedostaje się do osocza. Wolne jony żelaza przechwytywane są przez apotransferynę osocza zanim uszkodzą tkanki, czego miarą jest wzrost TSAT.

Cel pracy. Celem badania była ocena u pacjentów dializowanych zmian wysycenia transferyny po dożylnej suplementacji izomaltozydu 1000 żelaza (III).

Materiał i metody. Miarą zmian stężenia apotransferyny były różnice TSAT. Badanie przeprowadzono w dwóch ośmioosobowych grupach pacjentów hemodializowanych z powodu schyłkowej niewydolności nerek z wyjściowym TSAT < 35%. W pierwszej grupie podawano żelazo w dwóch dawkach po 100 mg w odstępie tygodniowym. W drugiej grupie pierwsza dawka izomaltozydu wynosiła 200 mg, druga 100 mg. Zmiany TSAT obserwowano 210 minut po podaży dożylnej izomaltozydu żelaza (III). Wyniki poddano analizie statystycznej z użyciem pakietu STATISTICA.

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Wyniki. Izomaltozyd 1000 żelaza (III) zarówno w dawce 100, jak i 200 mg powodował znamienny statystycznie, przejściowy wzrost TSAT. Po dawce 200 mg wartości TSAT były znamiennie wyższe w porównaniu z dawką 100 mg (p = 0,026264). W żadnym przypadku nie zaobserwowano jednak TSAT przekraczającego 60%. Nie stwierdzono też żadnych działań niepożądanych leku.

Wnioski. U pacjentów hemodializowanych dawki 100 i 200 mg izomaltozydu 1000 żelaza (III) powodują umiarkowany, przejściowy wzrost wartości TSAT. Dawka 200 mg wydaje się bezpieczna tylko przy znacznym niedoborze żelaza.

INTRODUCTION

Erythropoiesis is an intricate, multistage process of differentiation of early pluripotent erythroid progenitors to mature enucleated erythrocytes. The process is dependent on numerous exogenous and endogenous factors, such as iron homeostasis, hypoxia, stress, growth and transcription factors (1). As erythropoietin is one of the strongest molecules stimulating erythropoiesis, its low production in diseased renal tissue may explain why anaemia is a prevalent complication of chronic kidney disease (CKD). However, iron deficiency-limited erythropoiesis is a compelling problem, contributing to the development of anaemia in chronic kidney disease and limiting efficacy of treatment with erythropoiesis stimulating agents (ESAs).

It is estimated that 2.4 x 10^6 new erythrocytes should be produced each second to maintain adequate haematocrit in 5 L of blood of a healthy adult individual (2). Therefore, nearly 80% of average 25 mg of daily iron requirement is used for erythropoiesis (3). In physiological conditions daily intake of iron ranges from 10 to 15 mg and the maximum absorption is about 20%, thus normal diet provides only 2-3 mg of iron. The remaining part comes in greatest proportion from effete erythrocytes undergoing eryptosis (2). Iron deficiency has deleterious impact not only on tissue oxygenation through impaired haemoglobin synthesis, but also on various metabolic processes including accumulation of muscle energy or oxygen storage in myoglobin, neuron myelination, and DNA synthesis (4). According to American data from the National Health and Nutritional Examination Survey (NHANES III) 60-73% of persons with an estimated glomerular filtration rate < 60 ml/min/1.73 m^2 are iron deficient, while iron deficiency anaemia affects 8.8% of the general world population (5, 6). Iron depletion is even more accentuated in patients with end-stage renal failure on maintenance haemodialysis, where blood loss during the procedure, frequent blood sampling and occult or overt gastrointestinal bleeding may diminish scant iron stores. Moreover, iron malabsorption may be exacerbated by poor appetite, low-protein diet and various drugs frequently used in CKD patients (proton pump inhibitors, phosphate binders). Despite absolute iron deficiency in CKD patients, functional iron deficiency (FID) is also prevalent. According to Macdougall's definition, FID is a state in which there is insufficient iron incorporation into erythroid precursors in the face of apparently adequate iron stores (7). This applies to the partial block in iron transport being the major cause of anaemia of chronic disease observed in inflammatory, infectious and malignant diseases, and to the second type of FID frequently occurring when erythroid marrow is stimulated with ESAs (8). Albeit multifactorial, both absolute and functional iron deficiencies may be partly assigned to impaired hepcidin – ferroportin axis.

Hepcidin and ferroportin are two crucial proteins that in cooperation with hemojuvelin, hephaestin, iron transporter DMT1 and duodenal cytochrome B (Dcytb) regulate plasma iron concentration (9). Ferroportin is the only known mammalian iron exporter (10). This basolateral transmembrane efflux channel in combination with ferroxidases (hephaestin, ceruloplasmin) enables absorption of ferric ions from duodenal enterocytes. Apart from that, ferroportin facilitates transfer of iron from hepatocytic storage to plasma and retrieval of iron from macrophages of the mononuclear phagocyte system, which phagocyte senescent erythrocytes. Hepcidin in turn, is a peptide hormone produced by hepatocytes in response to increased iron levels. In a negative feedback loop hepcidin causes internalization and ubiquitination of ferroportin, thus limiting intestinal iron absorption and causing iron entrapment in macrophages, hepatocytes and enterocytes (11, 12). Decreased iron absorption is the only known mechanism preventing from iron overload, for iron loss is not regulated in any defined pathway and may occur mainly through cell shedding or bleeding (11, 13). Hence, hepcidin expression is modulated by various endogenous and exogenous factors. Tissue iron stores and transferrin saturation regulate hepcidin transcription by BMP-SMAD pathway with hemojuvelin as a cofactor. Inflammation is another hepcidin transcriptional regulator, through the JAK-STAT3 pathway initiated by Il-6 (12, 13). As a consequence, in numerous patients with chronic renal failure, hepcidin levels are elevated due to an underlying inflammatory process (14). Moreover, in the end-stage renal failure hepcidin may be not efficiently eliminated, neither by kidneys nor by dialysis. In addition, the dialysis procedure may initiate inflammatory-mediated hepcidin transcription (14). Therefore in CKD patients hepcidin levels consecutively rise, compromising iron homeostasis.

Taking into account all the pathophysiological aspects of iron absorption and storage in patients with CKD, screening for iron deficiency should be performed, and iron supplementation considered, especially in the view of poor responsiveness to ESA treatment.

Nevertheless, iron supplementation has certain disadvantages. Oral supplementation in CKD patients is frequently inefficient, while intravenous supplementation is associated with various adverse effects, including anaphylactic reactions and tissue toxicity. Iron is a redox-active transition metal and it may exist in two ionic states: ferrous – Fe(II), and ferric – Fe(III), thus enabling electron transfer among molecules. This redox activity is potentially damaging and free, unbound iron easily triggers it. Human organism limits free forms of iron ions by binding them to transferrin in plasma or to ferritin intracellularly, before incorporating it into heme and non-heme proteins (15, 16). Transferrin with two iron-binding sites may exist as four molecular forms – apotransferrin, monoferric A and B transferrin, and diferric transferrin, depending on the level of saturation (16). The saturation of transferrin is calculated with an equation:

TSAT = Fe (mg/dl)/TIBC(mg/dl) x 100%

and in physiological conditions ranges from 20 to 45%. Erythroblasts most efficiently utilize iron with TSAT 30-60%. Above this range macrophages intercept iron bound to transferrin and store it in ferritin (17, 18). Higher levels of transferrin saturation correspond to formation of significant amounts of non-transferrin bound iron (NTBI). This pool of free iron is supposed to be responsible for tissue toxicity and cell damage. NTBI via the Fenton and Haber-Weiss reactions, may induce oxidative stress by promoting formation of reactive oxygen species (ROS) that subsequently cause increased lipid, protein and carbohydrate peroxidation (19, 20). This in turn might result in disruption of cell membranes leading to their increased permeability or even cell lysis (4). In addition, iron dose-related damage to components of DNA was described (21). NTBI is absorbed mainly by the liver, however, an unregulated NTBI uptake was also observed in the cells of the endocrine system, the brain, lungs, or the heart (22, 23). Emerging data link NTBI to organ damage in iron-overload disorders, such as haemochromatosis or thalassaemia (24). Higher levels of TSAT, an evidence for reduced transferrin potential to buffer free iron pool, were associated with increased frequency of stomach cancer in women and colon cancer in men (25). Nevertheless, neither the pathophysiological consequences of short term increase of TSAT, observed after intravenous iron supplementation, nor long-term toxicity of repeated doses of iron preparations are known.

Currently in Europe there are several preparations used for intravenous iron supplementation: iron gluconate, ferric carboxymaltose, iron sucrose, iron low-molecular dextran, isomaltoside 1000, ferumoxytol. All these substances differ in size of molecules, pharmacokinetic and pharmacodynamic characteristics. Depending on the thermodynamic stability of the preparation, the pool of the labile iron, that is loosely attached to the transporting medium, and therefore immediately bound to transferrin after injection, is divers (4).

AIM

As injection of iron preparations results in the TSAT increase to various degrees, the aim of this study was to assess, how iron (III) isomaltoside 1000, a relatively new, stable iron preparation used in haemodialyzed patients as a part of routine supplementation, influences the saturation of transferrin.

MATERIAL AND METHODS

This observational study was performed on data from two groups of patients with anaemia treated with maintenance haemodialysis for end-stage renal failure. Each group comprised 8 patients with baseline TSAT < 35%. Two single weekly doses of 100 mg iron (III) isomaltoside 1000 were administered in one group (group 100/100). In the second group, 200 mg iron (III) isomaltoside 1000 was administered as the first weekly dose, and 100 mg as the second (group 200/100). Baseline total blood count, reticulocyte level, ferritin, transferrin and CRP concentrations were measured to exclude contraindications to iron administration and to calculate baseline TSAT. The changes in TSAT were measured 210 minutes after administration of each dose of iron (III) isomaltoside 1000, which is a standard procedure at the Department. This time span between measurements was based on previous studies, in which the point of maximum TSAT value after intravenous administration of iron gluconate was estimated (26).

The results were analysed with the use of the STATISTICA 13 software. The normality of the distribution of the variables and the differences between the variables of the paired data was checked with the Shapiro-Wilk test. For paired data in the intragroup analysis, the Student t-test was used when the assumption of normal distribution of the differences was fulfilled, and when the assumption was violated, the Wilcoxon test was used. ANOVA and ANCOVA tests served for intergroup analysis. The significance level was set to 0.05.

RESULTS

Initial TSAT values are presented in table 1.

After the first infusion of 100 mg of iron (III) isomaltoside 1000 in the 100/100 group the TSAT values increased by mean 14.4 ± 5.18% in comparison with baseline values (p = 0.0001). One week after the first dose a decrease in transferrin saturation was observed, so before the second dose of 100 mg the TSAT values reached the levels similar to the baseline values (p = 0.527). Following the second infusion of 100 mg of iron (III) isomaltoside in the 100/100 group, the TSAT values significantly increased by a similar value of 12 ± 6.07% (p = 0.00065). There was no statistically significant difference between TSAT values after the first and the second dose of the preparation in this group.

In the 200/100 group of patients, a significant increase by 22.22 ± 6.09% in the TSAT values was

Table 1. TSAT values measured before iron supplementation and 210 minutes after injection (partly published by our group elsewhere (32)).

TSAT before and after injection of iron III isomaltoside, iron sucrose or low-molecular dextran iron			
Group/parameter	**TSAT before injection [%]**	**TSAT 210' after injection [%]**	**ΔTSAT [%]**
100 mg iron III isomaltoside 1000 – 5% (mean value for three doses)	25.3 ± 8.2	40.4 ± 7.6	15.1 ± 6.5
200 mg iron III isomaltoside 1000 – 5%	22.1 ± 5.7	44.3 ± 8.0	22.2 ± 6.1
50 mg iron sucrose	19.0 ± 5.6	38.6 ± 7.0	19.6 ± 4.8
100 mg iron LMW-dextran	23.0 ± 5.2	32.0 ± 5.6	9.2 ± 2.6
200 mg iron LMW-dextran	28.4 ± 9.6	46.8 ± 15.4	18.5 ± 21.4
No iron injection	28.0 ± 15.8	26.3 ± 15.0	-1.7 ± 3.37

observed after the infusion of 200 mg of iron (III) isomaltoside 1000 ($p = 0.000017$). In a week the values significantly decreased reaching values comparable to the baseline TSAT ($p = 0.68$). After the second dose of 100 mg of iron (III) isomaltoside the TSAT values raised by 18.5 ± 7.39% ($p = 0.000199$) – insignificantly more as compared to the second 100 mg dose in the 100/100 group (as proved by the intergroup analysis given below).

Intergroup analysis

The baseline TSAT values did not differ significantly between the groups neither before the first (0.89) nor the second dose of 100 mg iron (III) isomaltoside 1000 (0.69). The TSAT values after iron infusion correlated with baseline values. No other association among variables assessed was observed. The ANCOVA analysis with baseline TSAT as a confounder showed that TSAT values after 200 mg isomaltoside were significantly higher in comparison to the first group receiving 100 mg of iron (III) isomaltoside 1000 ($p = 0.026$). There was no statistically significant difference in TSAT values between the groups after the second dose of 100 mg of the preparation. In neither group any immediate or late adverse events of iron (III) isomaltoside 1000 were observed.

DISCUSSION

Anaemia in chronic kidney disease has always been a substantial issue, as it results in increased mortality associated with left ventricle hypertrophy, cardiovascular events, and significantly lower quality of life, due to fatigue, reduced physical performance, cognitive impairment, sleep and sex disorders (27-29).

Since 1930' when the first intravenous iron supplementation with highly toxic iron-oxyhydroxide complex was introduced, the iron preparations substantially evolved reaching high levels of safety and efficacy (30). Still, balancing between iron deficiency and excess, it is extremely hard to propose one concise algorithm of iron supplementation. According to the statement of the Polish Society of Nephrology, in haemodialysis patients with absolute iron deficiency, 125 mg of iron gluconate or 100 mg of iron sucrose may be administered during 8 or 10 consecutive dialysis sessions, respectively. As an alternative, up to 1000 mg of carboxymaltose, ferumoxytol or iron (III) isomaltoside 1000 in a single dose may be introduced. In the strategy preventing from iron deficiency, lower doses of these preparations should be administered regularly – once in a week or once in a fortnight – to reach TSAT values between 20 and 50% and ferritin concentration between 100 and 800 ng/ml (31).

Based on the results from previous studies conducted at our Department (tab. 1), it is noteworthy, that 200 mg of iron (III) isomaltoside 1000 raised transferrin saturation to the mean 44.29 ± 7.95 which was comparable to the values after 200 mg of the low-molecular weight (LMW) dextran preparation. However, after injection of 100 mg of the medication transferrin saturation reached greater values than after 100 mg of iron LMW-dextran (39.52 ± 8.87 vs 32.0 ± 5.6), despite similar baseline values (32). On the other hand, TSAT values after 100 and 200 mg isomaltoside 1000 were comparable to the ones observed after only 50 mg of iron sucrose injection. The maximum TSAT level observed after infusion of 50 mg of iron sucrose was 51.6%; 38.4% after 100 mg of iron LMW-dextran, and 72.4% after 200 mg of iron LMW-dextran (unpublished data from our Department). In the two iron (III) isomaltoside 1000 groups, the maximum TSAT value was 57.52% after the dose 100 mg and 56.27% after the dose 200 mg, thus reflecting rather high stability of the preparation.

Nevertheless, this study has certain limitations. As this was a preliminary observation study the groups were relatively small, and the results need to be confirmed in larger population. The time span for measurement of maximum TSAT was based on studies with the iron gluconate. This unifies protocol with the previous studies conducted at our Department and enables comparison among groups, still, the exact dynamics, of TSAT after iron (III) isomaltoside 1000 infusion, especially the peak of TSAT, in haemodialysis patients is not known.

CONCLUSIONS

TSAT values observed after infusion of iron (III) isomaltoside 1000 are strongly associated with the baseline values of transferrin saturation. Although the TSAT increase is supposedly dose-dependent,

as the mean rise in transferrin saturation was significantly greater after 200 mg than after 100 mg, iron (III) isomaltoside 1000 does not cause oversaturation of transferrin beyond 60%, neither with 100 mg, nor with 200 mg of elementary iron. In addition, the increase in TSAT values is short-lasting. This suggests that iron (III) isomaltoside 1000 may be safely administered to stimulate iron-deficient erythropoiesis, especially in patients with deep iron deficiency.

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