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Effect of methoxy polyethylene glycol-epoetin beta on oxidative stress in predialysis patients with chronic kidney disease

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Background: There is data in the literature indicating increased oxidative stress in chronic kidney disease (CKD). Erythropoiesis-stimulating agents (ESAs), which are commonly used to treat anemia in patients with CKD, seem to have an antioxidant action, which could be a part of nephroprotection. The aim of the current study was to investigate the effect of a long half-life ESA, methoxy polyethylene glycol-epoetin beta (Mircera), on some markers of oxidative stress in predialysis patients with CKD.

Material/Methods: Peripheral blood was collected from 28 predialysis CKD patients 2 times, before Mircera treatment and after achieving target hemoglobin (Hb), and 15 healthy subjects (control group). Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) activity in erythrocytes were measured according to commonly used methods as a function of the antioxidant defense system. To assess reactive oxygen species (ROS) production, malondialdehyde (MDA) concentration in erythrocytes and in plasma was measured according to a commonly used method.

Results: SOD, GSH-Px, and CAT activity were similar, but plasma and erythrocyte MDA concentrations were significantly higher in CKD patients before ESA treatment in comparison to the control group. SOD, GSH-Px, and CAT activity was significantly higher, but plasma and erythrocyte MDA concentrations were significantly lower, in CKD patients after ESA treatment in comparison to these patients before treatment. We did not find a significant correlation between Hb concentration and SOD, GSH-Px, and CAT activity and plasma, as well as erythrocyte MDA concentrations. Analysis of all investigated groups showed a significant negative correlation between Hb concentration and plasma MDA concentration.

Conclusions: Our results suggest that treatment of anemia with methoxy polyethylene glycol-epoetin beta may inhibit oxidative stress in predialysis patients with CKD by enhancing the antioxidant defense system and reducing ROS production.

Key words: chronic kidney disease (CKD) • erythropoiesis-stimulating agents •oxidative stress • anemia

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Background

Patients with chronic kidney disease (CKD) show a very high cardiovascular morbidity and mortality [1–4]. Oxidative stress and inflammation seem to be links between CKD and cardiovascular complications [5,6]. Oxidative stress and rapid progression of atherosclerosis play an especially important role in increased risk of cardiovascular complications in CKD patients [7]. The mechanisms responsible for enhanced oxidative stress in CKD patients include increased production of reactive oxygen species (ROS) and dysfunction of the antioxidant defense system [8]. Increased serum concentration of the main lipid peroxidation product, malondialdehyde (MDA), in plasma and erythrocytes indicates overproduction of ROS in CKD patients [9,10]. Data in the literature confirm dysfunction of the antioxidant defense system decreases activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) in CKD patients [10,11]. Higher CKD stage is associated with higher oxidative stress. Glomerular filtration rate (GFR) has been reported to be inversely associated with MDA concentration and positively correlated with SOD activity [12]. Many published studies show that renal anemia plays a very important role in pathogenesis of increased oxidative stress in CKD patients; higher degree of renal anemia is associated with stronger oxidative stress [9,13]. Erythropoiesis-stimulating agents (ESAs), which are widely used in anemia treatment in CKD patients, seem to have renoprotective effects and slow progression of CKD, in addition to improving patient outcomes and quality of life [14,15]. Most publications on these renoprotective effects concern short half-life ESAs with possible renoprotective mechanisms as antiapoptotic, anti-inflammatory, and antioxidant effects [14–16]. Some evidence indicates that ESA treatment caused increased activity of erythrocyte antioxidative enzymes and decrease of plasma and erythrocyte MDA concentrations [9,17,18]. Long half-life ESAs such as darbepoetin-α and especially methoxy polyethylene glycol-epoetin beta seem to be the best choice to achieve this long and slow renoprotective effect in predialysis patients with CKD [19,20]. There is scant data about the influence of anemia treatment with darbepoetin-α on oxidative stress in CKD patients [21]. The lack of data in the literature concerning the influence of methoxy polyethylene glycol-epoetin beta on oxidative stress in predialysis CKD patients was the reason for conducting this study.

Material and Methods

Patient population

Thirty predialysis patients (20 men and 10 women) with anemia and CKD in stage IV and V treated with methoxy polyethylene glycol-epoetin beta (Mircera, Roche, Basel, Switzerland) were enrolled in the study. Causes of CKD were: hypertonic nephropathy (40%), chronic tubule-interstitial nephritis (23%), chronic glomerulonephritis (20%), and polycystic kidney disease (17%). The control group included 15 volunteers (10 men and 5 women) without CKD (eGFR >60 ml/min, normal hemoglobin level, normal urine analysis, and kidney ultrasound).

CKD patients with hemoglobin (Hb) level <10 g/dl and eGFR <30 ml/min, after excluding bleeding, iron deficiency, hemolysis, infection, and severe secondary hyperparathyroidism, received a subcutaneous injection of Mircera in doses of 0.6 μg/kg once monthly. Treatment was continued until reaching the target Hb level of 11–12 g/dl, achieved by 28 patients who were enrolled in the second part of the study. Average treatment time was 227 days (range, 108–428 days). The average Mircera dose was 50 μg/monthly (from 30 to 75 μg). We excluded patients with diabetes, blood transfusion in the past 3 months, acute infection, chronic infection (hepatitis B and C), immunological disease, immunosuppressive therapy or history of malignancy. More data from patients who achieved target Hb and the control group are presented in Table 1.

The study was approved by the Research Ethics Committee of the Medical University of Lodz – number RNN/97/09/KB. Only patients who signed informed consent were included in the study.

Measurement of some markers of oxidative stress

Erythrocytes play a key role in maintenance of the systemic and local antioxidant defense system; therefore, evaluation of SOD, GSH-Px, and CAT in erythrocytes is a reliable method for use in studying this system [10,21]. Similarly, increased MDA concentration in plasma and erythrocytes is well known as a marker of ROS overproduction and increased lipid peroxidation, and is strongly connected with oxidative stress [22,23]. Therefore, in our study, we assessed activity of SOD, GSH-Px, and CAT in erythrocytes and MDA concentration in plasma and erythrocytes as markers of oxidative stress.

Peripheral blood was drawn from CKD patients 2 times: before treatment with Mircera and after achieving target Hb. Hb level along with the other routine laboratory tests was evaluated monthly. Peripheral blood was drawn once from healthy volunteers. Venous blood was collected into heparinized tubes and centrifuged for 15 min at 1500 × g. Plasma was separated and the erythrocytic mass was washed 3 times with a double volume of physiological saline solution and then hemolyzed. In the hemolysate, SOD activity was determined by the adrenaline method according to Misra and Fridovich [24]; GSH-Px activity was determined by the method with Ellman's reagent of Sedlak and Lindsay [25], as modified by Little and O'Brien [26] with the use of cumene hydroperoxide as a substrate; and CAT activity was determined by the spectrophotometric

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Table 1. Characteristics of Hb, creatinine and eGFR in examined subjects.

	Patients before treatment (n=28) (Me; 25–75%)	Patients after treatment (n=28) (Me; 25–75%)	Control group (n=15) (Me; 25–75%)
Hb (g/dl)	9.6 (9.1–10.0)	11.6 (11.1–12.0)	14.4 (13.3–14.9)
Creatinine (µmol/l)	300.0 (249–395)	298.0 (239–396)	90.0 (77–108)
eGFR (MDRD)	16.4 (13.9–21.8)	16.6 (14.0–23.3)	65.0 (63–74)

Table 2. Results of patients with CKD before ESA treatment and control group.

	CKD patients before treatment (n=28)	Control group (n=15)	Significance
Hb (g/dl)	9.6±0.7	14.4±1.1	P<0.0001
Creatinine (µmol/L)	300±28	90±7.4	P<0.0001
eGFR (MDRD)	16.4±1.2	65±5.8	P<0.0001
SOD [U/gHb]	2145±617	2460±514	NS
CAT [U/gHb]	19.3±8.5	22.3±4.5	NS
GSH-Px [U/gHb]	82.2±25.4	92.4±20.5	NS
MDA RBC [µmol/gHb]	0.27±0.14	0.20±0.04	P=0.025
MDA plasma [µmol/ml plasma]	0.58±0.25	0.40±0.18	P=0.015

Data presented as mean ±SD. Significance between groups was estimated based on Student's t-test for unpaired data.

method for measuring the breakdown of hydrogen peroxide of Beers and Sizer [27]. The activities of these enzymes were expressed in units per gram of hemoglobin (U/gHb). Hb concentration was determined using standard reagents (Biomed, Poland). The degree of lipid peroxidation in erythrocytes and plasma was expressed as the concentration of thiobarbituric acid reactive substances (TBARS), mainly malondialdehyde (MDA), according to Placer et al. [28]. MDA concentration in erythrocytes (MDA RBC) is expressed in µmol/gHb, and in plasma (MDA Plasma) in µmol/ml plasma.

Statistical analysis

Data are presented as mean ±SD. Evaluation of statistical significance was performed by t-test for paired and unpaired data. Correlation between Hb concentration and investigated markers of oxidative stress was evaluated by calculation of Pearson r correlation coefficient. Statistical significance was assumed at p value <0.05.

Results

The results concerning patients with CKD before ESA treatment and the control group are shown in Table 2.

SOD, CAT, and GSH-Px activity were similar between CKD patients before ESA treatment and the control group. MDA concentrations in erythrocytes and in plasma were significantly higher in patients with CKD before ESA treatment in comparison to the control group.

The results concerning patients with CKD after ESA treatment and the control group are shown in Table 3.

There were no differences in activity of SOD, CAT, and GSH-Px in CKD patients after ESA treatment and the control group. MDA concentrations in erythrocytes and in plasma were similar in CKD patients after ESA treatment in comparison to the control group.

The results concerning patients with CKD before and after ESA treatment are shown in Table 4.

Hb concentration after ESA treatment was significantly higher but creatinine concentration and eGFR were comparable to those before ESA treatment. Activity of SOD, CAT, and GSH-Px was significantly higher after ESA treatment, but MDA concentrations in erythrocytes and in plasma were significantly lower after ESA treatment in comparison with those before treatment.

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Table 3. Results of patients with CKD after ESA treatment and control group.

	CKD patients after treatment (n=28)	Control group (n=15)	Significance
Hb (g/dl)	11.6±0.6	14.4±1.1	P<0.0001
Creatinine (µmol/L)	298±31	90±7.4	P<0.0001
eGFR (MDRD)	16.6±1.4	65±5.8	P<0.0001
SOD [U/gHb]	2440±693	2460±514	NS
CAT [U/gHb]	23.3±10.3	22.3±4.5	NS
GSH-Px [U/gHb]	92.5±21	92.4±20.5	NS
MDA RBC [µmol/gHb]	0.18±0.05	0.20±0.04	NS
MDA plasma [µmol/ml plasma]	0.43±0.2	0.40±0.18	NS

Data presented as mean ±SD. Significance between groups was estimated based on Student's t-test for unpaired data.

Table 4. Results of patients with CKD before and after ESA treatment.

	CKD patients before treatment (n=28)	CKD patients after treatment (n=28)	Significance
Hb (g/dl)	9.6±0.7	11.6±0.6	P<0.0001
Creatinine (µmol/L)	300±28	298±31	NS
eGFR (MDRD)	16.4±1.2	16.6±1.4	NS
SOD [U/gHb]	2145±617	2440±693	P=0.02
CAT [U/gHb]	19.3±8.5	23.3±10.3	P=0.0058
GSH-Px [U/gHb]	82.2±25.4	92.5±21	P=0.01
MDA RBC [µmol/gHb]	0.27±0.14	0.18±0.05	P=0.0057
MDA plasma [µmol/ml plasma]	0.58±0.25	0.43±0.2	P=0.0028

Data presented as mean ±SD. Significance between groups was estimated based on Student's t-test for paired data.

The correlation between Hb concentration and markers of oxidative stress is shown in Table 5.

We did not find a significant correlation between Hb concentration and activity of SOD, CAT, GSH-Px, and MDA concentration in erythrocytes and in plasma in CKD patients. Analysis of all investigated groups showed a significant negative correlation between Hb concentration and plasma MDA concentration.

Discussion

Our study shows that SOD, CAT, and GSH-Px activity was similar in CKD patients before methoxy polyethylene glycol-epoetin beta treatment to that of the control group. In addition we observed that MDA concentrations in erythrocytes and in plasma were significantly higher in patients with CKD before treatment in comparison to the control group. Our findings, similar to those reported in the literature, but concerning short half-life ESAs, indicate that CKD is connected with increased oxidative stress. The literature regarding CKD patients indicates decreased SOD, CAT, and GSH-Px activity [2,10,21] and increased MDA concentrations in plasma and erythrocytes as a result of increased ROS production [2,18,21]. Increased ROS production and a reduced antioxidant defense system, caused by oxidative stress, play an important role in pathogenesis of accelerated atherosclerosis, hypertension, and cardiovascular disease [7,29,30], which are the major cause of death in patients with CKD [2,31–33]. The pathogenesis of oxidative stress in CKD pre-dialysis patients includes uremic toxins, malnutrition, and intravenous iron supplementation [34]. There seems to be a close relationship between oxidative stress and inflammation in CKD. Inflammation, immunological cell activation, and release of cytokines are connected with ROS overproduction

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Table 5. Correlation between Hb concentration and markers of oxidative stress.

	Hb before treatment (n=28)	Hb after treatment (n=28)	Hb before and after treatment together (n=56)	Hb before and after treatment and control group together (n=71)
SOD [U/gHb]	0.044	–0.048	0.190	0.149
CAT [U/gHb]	0.027	0.119	0.218	0.151
GSH-Px [U/gHb]	–0.136	0.048	0.153	0.097
MDA RBC [µmol/gHb]	0.275	0.155	–0.223	–0.213
MDA plasma [µmol/ml plasma]	0.109	0.129	–0.221	–0.294*

Pearson r correlation coefficient values; * $p<0.05$.

and could be triggers of oxidative stress in CKD [35,36]. Recent data indicate a relationship between the progression of CKD and the activities of GSH-Px, SOD, CAT genotypes, and oxidative stress [37]. Some data in the literature indicate a link between oxidative stress and anemia, which is very common in CKD patients. Hypoxia due to anemia can cause overproduction of mitochondrial ROS and enhance oxidative stress [38]. In the management of renal anemia, short half-life epoetin alfa or beta and long half-life darbepoetin-α or methoxy polyethylene glycol-epoetin beta have been successfully used, both in patients treated with dialysis and in predialysis [39]. Erythropoietin (EPO), through its main action (stimulation of red blood cell precursor with subsequent correction of anemia, improvement of blood flow and tissue oxygenation), may inhibit oxidative stress, apoptosis, and tissue fibrosis, which in turn may slow down the progression of CKD and decrease cardiovascular morbidity and mortality [40,41]. There is some evidence that anemia treatment with EPO is associated with improvement of oxidative stress by reducing ROS production and by improving the antioxidant defense system [9,13,18,21]. In the available literature, we found no data regarding the effect of methoxy polyethylene glycol-epoetin beta on oxidative stress in CKD patients. The results of our study indicate that CKD patients treated with methoxy polyethylene glycol-epoetin beta, after reaching the target hemoglobin level, showed a significantly higher activity of SOD, CAT, and GSH-PX and significant reduction in plasma and erythrocyte MDA concentrations in comparison to CKD patients before ESA treatment. We did not observe a significant correlation between Hb concentrations in all investigated groups and activities of SOD, CAT, and GSH-Px, and with erythrocyte MDA concentrations. Analysis of all investigated groups showed a significant negative correlation between Hb concentration and plasma MDA concentration only. Our findings indicate that anemia treatment with methoxy polyethylene glycol-epoetin beta may reduce ROS overproduction and lipid peroxidation and enhance the antioxidant defense system in predialysis CKD patients. There are no data on the possible mechanisms of inhibition of oxidative stress by methoxy polyethylene glycol-epoetin beta in the literature. Most likely, these mechanisms are similar to those described in the case of short half-life ESAs [16]. Proposed mechanisms of antioxidative effects of EPO include: increasing heme oxygenase-1 expression [42,43], induction of antioxidative enzymes [21], reduction of ROS production [9,18], depleting body iron, and increasing the number of circulating young red blood cells with increased levels of erythrocyte antioxidative enzymes [44]. It is worth noting that in our study there was no deterioration of renal excretory function during or after reaching the target level of Hb compared to the value before ESA treatment. Perhaps this was because the average duration of treatment required to achieve the target Hg level was relatively long and the applied doses of ESAs were small. A search of the literature shows that the most favorable renoprotection is achievable using the slow correction of anemia with a lower dose of preferably long half-life ESAs [45,46].

Conclusions

The results of our study suggest that treatment of anemia with methoxy polyethylene glycol-epoetin beta may inhibit oxidative stress in CKD pre-dialysis patients due to enhancing the antioxidant defense system and reducing ROS production. The treatment of anemia with methoxy polyethylene glycol-epoetin beta in predialysis CKD patients could be associated with the nephroprotective action arising from the compensation of anemia, improvement of blood circulation and oxygenation of tissues and organs, as well as from the inhibition of oxidative stress. Further intensive research on large groups of patients is needed to confirm the nephroprotective properties of methoxy polyethylene glycol-epoetin beta and to establish the mechanisms of this nephroprotection.

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