MORPHOLOGY, PATHOLOGY, PHYSIOLOGY

Cite as: Archiv EuroMedica. 2022. 12; 3: e1. DOI 10.35630/2199-885X/2022/12/3.31

Received 21 April 2022;
Received in revised form 15 May 2022;
Accepted 16 May 2022

INTERPLAY BETWEEN PARAMETERS OF THE HAEMOSTATIC SYSTEM AND URINE FORMATION IN RATS UNDER EXPERIMENTAL MERCURY INTOXICATION. PREVENTIVE OPTIONS.

Vadim Brin [1,2] ✉, ***Elmira Gagloeva*** [1]

[1] *North Ossetian State Medical Academy, Vladikavkaz;*
[2] *The Institute for Biomedical Research – a Branch of the Vladikavkaz Research Centre of the Russian Academy of Sciences, Vladikavkaz, Russia*

✉ vbbrin@yandex.ru

UDC 546.74:616.-005.1-08

ABSTRACT

We have explored the effects of melatonin on the interplay between parameters of the haemostatic system and the disruption in basic processes of urine formation under chronic sublimate intoxication.

The prophylactic administration of melatonin was performed at a dose of 5 mg/kg along with the intragastric administration of mercury chloride at a dose of 0.5 mg/kg for two months. The use of melatonin helped reduce the Impairment in vascular-platelet and coagulation haemostasis and in the activity of the anticoagulant and fibrinolytic systems, and contributed to the reduction in thrombinaemia. Observed changes correlated with the restoration of urine formation and lipid peroxidation processes and of the activity of antioxidant blood enzymes. The results of the study suggest that melatonin can be recommended for further studies aimed at developing tools for correcting haemostasis associated with exposure to heavy metal compounds.

Keywords: melatonin, mercury, haemostasis, osmolarity.

INTRODUCTION

The haemostatic system is an important evolutionary protective mechanism of the body, including the endothelium, plasma proteases, thrombin, and factor XIIa. The components of the coagulation system are linked with the function of proteolytic systems, such as fibrinolytic, kallikrein-kinin, complement, etc. [1,2,3]. It has been shown that almost any stress may impact the function of the coagulation system, more often towards increasing it. [4]. It appears relevant to explore the relationship between the state of the haemostatic system and the development of renal pathology. The latter tends to increase sharply in case of the increase in the toxic load of the environment on the body. [5].

Modern treatment regimens for chronic kidney disease necessarily involve the correction of the haemostatic system. Along with that, even in absence of renal pathology, the administration of anticoagulants may often lead to the development of anticoagulant-related nephropathy. [6]. Exploring and developing means of correcting the haemostatic system for future implementation of pathogenetic

therapy for toxic nephropathy appears highly relevant. Previously, it was shown that the use of the pineal hormone melatonin is effective in drug-induced nephropathy [7], helps to restore the urinary function of the kidneys under the toxic effects of mercury chloride [8]. At the same time, the possibility of prophylactic use of melatonin to correct the haemostatic system in toxic sublimate intoxication, as well as the role of haemostasis in the mechanisms of restoring the urinary function of the kidneys, is yet to be established.

The **objective** of the present study was to explore the effect of melatonin on the relationship between changes in the parameters of the haemostatic system and disorders in the processes of urination in chronic mercury chloride intoxication.

MATERIALS AND METHODS

The experiments were performed in 70 Wistar rats weighing 300-350g. The solution of mercury chloride was injected through a tube into the stomach at a dose of 0.5 mg/kg (1-9) along with intragastric administration of the solution of melatonin (Melaxen) at a dose of 5 mg/kg for two weeks, one and two months (8). At the end of the experimental period, rats were examined for indicators of vascular-platelet and plasma haemostasis, indicators of the functional state of the kidneys in six-hour spontaneous diuresis, as well as the activity of lipid peroxidation (LPO) processes. The following parameters were registered: platelet aggregation (ADP-induced, 10.0 μg/ml); activated partial thromboplastin time (aPTT); prothrombin time (PT); fibrin monomer polymerization time (FMPT), fibrinogen; antithrombin III (AT III); protein C; euglobulin lysis time (ELT), soluble fibrin monomer complexes (SFMCs) (4.1) (Equipment used included "Technology Standard" diagnostic kits (Russia), AR2110 aggregometer, CGL-2110 Solar turbidimetric coagulometer (Belarus). Creatinine and total protein concentration (Agat-Med, Russia) and osmolarity (Osmomat-2, Gonotec GmbH, Germany) were measured in urine and blood plasma. In the layers of kidney tissue, the concentrations of sodium (using ion-selective analyzer AEK-01 "Kverti-Med", Russia) and urea (following the methodology by S.G. Gasanov (1962) in our modification - rational proposal 241 and 242, dated 20.12.2006). The extraction of sodium from tissues was carried out using nitric acid. (0.75 N). To assess the intensity of LPO processes, the following parameters were measured: malondialdehyde (MDA) in erythrocytes, hydroperoxides (HP) (diene conjugates and diene ketones) in blood plasma, catalase activity (PV1251C spectrophotometer, Solar).

Statistical analysis was performed using Statistica 10.0 (StatSoft, Inc.) and Microsoft Excel 2010. Data is presented as median and IQR. Non-parametric Mann-Whitney U test was performed to analyse the differences between groups; Spearman correlation was used for analysing associations between numerical variables. Significance threshold was set at $p \leq 0,05$.

RESULTS AND DISCUSSION:

Mercury is a known nephrotoxic poison [5]. At the same time, given its excessive intake associated with modern environmental conditions, the toxicity affects almost all organs and systems. In people working with mercury for a long time, changes in the haemostatic system toeards hypercoagulation have been detected. [3,10]. However, the findings across several studies performed in vivo and ex vivo are inconsistent. While some [2,3] pointed to an increase in coagulation potential, one study failed to show alterations in parameters of haemostatic system even under exposure to mercury doses close to semi-lethal [11].

Our study in rats with intragastric administration of mercury chloride showed the development of procoagulant tendencies with simultaneous activation of the anticoagulant and fibrinolytic links of the haemostatic system already in the initial stages of the experiments (table 1.). In rats, after two weeks of intoxication, the degree of ADP-induced aggregation and the concentration of fibrinogen increased. Shortening of prothrombin time was detected. The activity of protein C and antithrombin III increased. In rats subjected to the prophylactic administration of melatonin, the hypercoagulable orientation of the processes of the haemostatic system remained unchanged. At the same time, melatonin prevented changes in the rate of prothrombinase formation, but the degree of disruption in the mechanisms of the anticoagulant system remained unchanged. What also remained unchanged was the increase in the plasma level of fibrinogen and the degree of ADP-induced thrombocyte aggregation. PT was reversed to control levels; and an increase in the activity of protein C was observed. However, antithrombin activity was significantly lower than that in rats with mercury intoxication, and did not differ from that in intact rats.

One month later, there was an increase in the rate of prothrombinase formation both along the external and internal pathways. The concentration of fibrinogen, the number of platelets and the degree of their aggregation increased. It had previously been shown that mercury ions are able to increase the

thromboplastic activity of blood cells by increasing the expression of phosphatidylserine on the outer surface of membranes [2,12]. A shortening of PT, APTT, spontaneous euglobulin lysis time and an increase in protein C activity were detected. Antithrombin activity did not differ from that in controls, but was lower than in rats after two weeks of the experiment. Intragastric administration of melatonin after one month contributed to a decrease in the degree of haemostatic changes. In rats subjected to melaxen, after one month, an increase in the activity of the haemostatic system was detected, but the changes were less pronounced than in rats with mercury intoxication. The number of platelets decreased compared to the group subjected to mercury alone, and did not differ from controls. The duration of APTT and PT did not change significantly. ELT was shortened, but the changes were less pronounced than in the group with mercury intoxication. The concentration of fibrinogen significantly exceeded control values, but was lower than in rats with mercury intoxication.

The results of the experiments carried out after two months from the introduction of mercury chloride clearly demonstrate an increase in the haemostatic potential. [4]. An increase in the degree of ADP platelet aggregation was observed, but their number decreased compared to that after one month and did not differ significantly from controls. Prothrombin time was prolonged; fibrin monomers polymerization time was shortened. The concentration of fibrinogen decreased significantly compared to values after one month, reaching control levels. At the same time, there was a depression of anticoagulant and fibrinolytic mechanisms. The activity of antithrombin decreased, ELT got prolonged. Thrombinaemia developed, and the content of soluble fibrin monomer complexes significantly increased.

Table 1. *The effect of melatonin on the parameters of the haemostatic system in rats with chronic mercury intoxication under experimental conditions.*

Parameter	**Controls**	**Mercury chloride**	**Mercury chloride+melatonin**
		1st line – after 2 weeks; 2nd line – after 1 month; 3rd line – after 2 months	
Platelet count, 10^9/l	560 (518÷599)	609(543÷632) 702,831(645÷730) *** 537(479÷597)	532(496÷580) 584(527÷632) ΔΔ 565(507÷628)
ADP-induced platelet aggregation, %	56,19 (51,27÷60,19)	63,62(60,34÷69,41) ** 74,89(71,07÷80,28) *** 71,64(66,12÷75,24) ***	62,45(59,15÷68,07)* 66,4(62,4÷71,5)**ΔΔ 64,2(61,3÷69,8)**Δ
aPTT, sec	28,73 (26,78÷29,69)	26,36(23,37÷28,75) 19,77(17,02÷22,59) *** 29.39(26,96÷32,69)	29,10(26,98÷30,88) 26,07(23,57÷28,75) ΔΔ 27,37(25,01÷29,47)
Prothrombin time, sec	18,23 (15,94÷21,25)	14,44 (12,08÷17,66) * 12,45 (11,64÷16,14) * 25,38(21,23÷27,57) **	12,45(11,64÷16,14)** 16,79(15,08÷18,58) Δ 22,03(19,67÷23,48)*Δ
Protein C activity, %	110,92 (92,22÷132,97)	151,25(136,74÷168,17)** 160,268(141,580÷175,805)** 116,543(90,381÷131,583)	146,29(128,65÷163,97)** 131,69(116,17÷149,80) Δ 113,70(97,10÷130,34)
Antithrombin III, %	100,86 (94,45÷105,98)	120,56 (113,23÷130,37) ** 96,79(89,02÷103,59) 70,12(57,40÷82,63) ***	104,73(93,03÷110,99) ΔΔ 102,96(94,04÷114,01) 85,48(74,72÷93,22)**Δ
Spontaneous euglobulin lysis time, min	506 (456÷560)	490(434÷543) 333(282÷406) *** 790(654÷878) ***	539,98(467,88÷577,92) 422,23(362,81÷467,70)*Δ 606,21(527,87÷692,48)*ΔΔ
Fibrinogen, g/l	2,09 (1,93÷2,18)	3,49(3,11÷3,93) *** 4,678 (3,943÷5,150) *** 2,511(1,790÷2,768)	2,66(2,28÷3,11)**ΔΔ 3,65(2,85÷4,08)***ΔΔ 2,01(1,64÷2,48)

Fibrin monomer polymerization time, RU	1,00 (0,91÷1,12)	1,08(0,98÷1,14) 0,996(0,89÷1,01) 0,74(0,63÷0,83) ***	0,98(0,88÷1,05) 1,01(0,90÷1,10) 0,94(0,79÷0,99) Δ
SFMCs, mg/100ml	3,22 (2,98÷3,65)	3,41(2,97÷3,88) 3,639(2,90÷4,31) 6,31(5,48÷6,89) ***	3,09(2,80÷3,38) 3,44(2,97÷3,89) 4,60(4,19÷5,51)***ΔΔ

Notes: p – level of statistical significance for the comparison of differences in parameters,
//*** - p≤0,05/0,01/0,001 – significance level for comparison of differences with the control group (intact),*
Δ/ΔΔ/ΔΔΔ - p≤0,05/0,01/0,001 – significance level for comparison of differences with mercury-only group
Data is presented as median(IQR).

The prophylactic administration of melatonin for two months contributed to the appearance of signs of stabilization of the haemostatic pattern and a decrease in the likelihood of developing a state of thrombotic readiness, described in rats with administration of mercury alone. This was supported by a decrease in the severity of changes in the SFMCs, the restoration of the activity of physiological anticoagulants and fibrinolysis (Table 1). Against the background of thrombocytopenia, platelet aggregation activity increased, but the changes were also less pronounced than in rats with sublimate intoxication. The experiments showed that intragastric administration of mercury chloride for two months leads to an impairment in the water excretory function of the kidneys and proteinuria (Table 2.), which is consistent with previously published studies [8]. Intoxication causes the development of polyuria due to a decrease in tubular water reabsorption.

Table 2. *The main indicators of the osmoregulatory function of the kidneys in rats under experimental conditions.*

Parameters	**Control**	**Mercury chloride**	**Mercury chloride+melatonin**
		1st line – after 2 weeks; 2nd line – after 1 month; 3rd line – after 2 months	
Diuresis (ml/h/100r)	0,074 (0,066÷0,087)	0,101(0,096÷0,109)*** 0,139(0,130÷0,147)*** 0,152(0,148÷0,168)***	0,111(0,099÷0,115)** 0,105(0,087÷0,116)**ΔΔΔ 0,131(0,122÷0,150)***Δ
Tubular reabsorption R_{H2O} (%)	99,60 (99,55÷99,64)	99,48(99,37÷99,50)*** 99,254(99,195÷99,276)*** 99,121(99,051÷99,144)***	99,42(99,38÷99,45)*** 99,43(99,33÷99,45)***ΔΔ 99,21(99,16÷99,25)***ΔΔ
Urine osmolarity Uosm (mOsm/ml)	1,771 (1,630÷1,855)	1,535(1,375÷1,745) 1,350(1,117÷1,413) *** 1,127(1,018÷1,185) ***	1,472(1,389÷1,674)** 1,43(1,34÷1,52)*** 1,57(1,35÷1,74)*ΔΔΔ
Free water clearance Cosm (ml/hr /100g)	0,454 (0,408÷0,498)	0,522(0,487÷0,634) * 0,596(0,548÷0,664) ** 0,587(0,564÷0,629) ***	0,555(0,484÷0,584)** 0,498(0,434÷0,578) 0,733(0,656÷0,783)***Δ
Fractional excretion of osmotically active	2,491 (2,182÷2,597)	2,898(2,325÷3,498) 3,520(3,211÷3,590)*** 3,567(3,160÷3,762)***	2,886(2,615÷3,631)** 2,857(2,557÷3,302)* 4,033(3,778÷4,675)***ΔΔ

agents, FE (%)			
Free water transport $T^{C}_{H_2O}$ (ml/h/100g)	0,382 (0,344÷0,411)	0,428(0,384÷0,530) 0,472(0,408÷0,527) * 0,432(0,421÷0,473) **	0,440(0,391÷0,482)* 0,397(0,338÷0,464) 0,574(0,529÷0,654)***ΔΔΔ
Proteinuria мг/мл	0,087 (0,070÷0,112)	0,156(0,076÷0,171) 0,581(0,482÷0,667) *** 1,005(0,821÷1,122) ***	0,131(0,100÷0,179) 0,434(0,311÷0,518)***ΔΔ 0,292(0,243÷0,484)***ΔΔΔ
Notes: see Table 1.			

Along with the increase in diuresis, an increase in the excretion of osmotically active substances and their excreted fraction was observed, which indicates a decrease in their tubular reabsorption. Despite the increase in osmotic blood purification, the concentration of osmotically active substances in urine was reduced, which, along with data on changes in the corticopapillary osmotic gradient of kidney tissue layers, could indicate a decrease in the renal concentrating function. [13]. However, in rats with normal glomerular filtration, diuresis and tubular transport of osmotically free water exceeded control levels (Table 2).

To explore the mechanisms behind the observed dynamics of the parameters of renal osmoregulatory function, we studied the electrolyte-urea profile of the layers of kidney tissues in rats. In particular, the content of sodium and urea in the layers of rat kidney tissues was studied, since they mainly create the osmolarity of the interstitium and, consequently, the functional state of the concentrating mechanism that determines the transport of osmotically free water from the lumen of the tubules to the interstitium of the renal medulla along the osmotic gradient [13]. Studies have shown that in experimental animals with intragastric administration of mercury chloride at a natural level of hydration, the concentration gradient of sodium and urea in the layers of the kidney from the cortex to the papilla did not significantly differ from that in control animals. Therefore, the decrease in tubular reabsorption of water, which provides the diuretic effect of mercury in rats with chronic intoxication, cannot be associated with the magnitude of the cortico-papillary gradient. An analysis of literature shows that mercury ions can covalently bind to the SH groups of proteins (Na+/K+-ATPase, aquaporin-1, etc.) of the membrane of epithelial cells that predominantly line the lumen of the proximal tubules of cortical nephrons [8,14]. Inhibition of proteins leads to a decrease in the transmembrane combined sodium-potassium transfer, as well as to blockade of water reabsorption processes. Mercury also binds to amino- and carboxyl groups of intracellular proteins to form stable nonfunctional mercury-protein complexes [5,9]. The inhibition of succinate dehydrogenase and other enzymes of energy metabolism in the mitochondria of epithelial cells of the proximal tubules is accompanied by the accumulation of excess amounts of succinic, glutamic and α-ketoglutaric acids, contributing to the development of irreversible toxic nephropathy [5,12,14]. Thus, a disruption in the processes of proximal water reabsorption can lead to an increase in the volume of fluid entering the distal tubules and collecting ducts, and with the same level of vasopressin and unchanged valuesof the osmotic gradient of the kidney, according to the results of our experiment, more osmotically free water can be absorbed from the increased amount of flowing fluid. Thus, an increase in diuresis may be accompanied both by an increased excretion of electrolytes not reabsorbed in the tubules and an increase in the reabsorption of osmotically free water.

Recent literature has widely covered the relationship between the activity of blood coagulation processes and thrombinaemia and an increase in the content of lipid peroxidation products in blood plasma, erythrocytes, leukocytes and platelets. According to the literature, the relationship between lipid peroxidation and haemostasis occurs mainly at the level of the first and second phases of blood coagulation; besides, the higher the concentration of lipid peroxides in platelets, the more actively while platelets are involved in this relationship [15].

Table 3. *The impact of mercury on the intensity of lipid peroxidation processes and the state of antioxidant defense system in rats under experimental conditions.*

Parameters		**Mercury chloride**	**Mercury chloride+melatonin**

	Control	*1st line – after 2 weeks; 2nd line – after 1 month; 3rd line – after 2 months*	
Malondialdehyde (MDA) (umol/l)	28,07 (27,00÷29,31)	27,30(26,30÷29,06) 34,21(31,73÷35,93) *** 38,14(36,22÷40,25) ***	31.1[29.3–32.7] 33.6[31.8–35.0]**Δ 32.0[31.5–33.9]*ΔΔΔ
Hydroperoxides (HP) (233nmol)	0,061 (0,050÷0,071)	0,075 (0,068÷0,085) * 0,091(0,081÷0,095) *** 0,079(0,068÷0,087) **	0.0744[0.0694–0.0867] 0.0758[0.0672–0.0837]ΔΔ 0.0429[0.0332–0.0494]***ΔΔ
Hydroperoxides (HP) (278nm)	0,049 (0,043÷0,053)	0,045(0,043÷0,05) 0,063(0,059÷0,072) ** 0,063(0,056÷0,069) **	0.0466[0.0321–0.0492]ΔΔ 0.0349[0.0252–0.0406] 0.0262[0.0235–0.0355]**Δ
Superoxide dismutase (SOD) (inhibition units,%)	71,21 (65,19÷76,57)	74,87(69,49÷81,26) 60,34(53,84÷66,94) ** 56,27(50,43÷64,05) **	76.22[69.35–80.50] 75.82[68.61–76.80]ΔΔ 63.90[56.17–67.57]*Δ
Catalase (*10-4IU/gHb)	7,26 (6,51÷8,10)	8,53 (7,55÷9,00) * 9,49(8,29÷10,28) * 4,32(3,69÷5,13) ***	7.36[6.40–8.02] 9.21[7.34–9.48]*ΔΔΔ 5.90[4.41–6.87]*Δ
Notes: see Table 1.			

The administration of mercury caused an increase in the concentration of malondialdehyde in erythrocytes (p≤0.01) and an increase in the level of hydroperoxides in blood plasma (p≤0.05 and p≤0.01) [8]. At the same time, a decrease in the activity of superoxide dismutase (p≤0.01) and catalase (p≤0.05) was detected, which is associated with the depletion of the enzymatic activity of antioxidants.

The preventive use of the natural antioxidant melaxen contributed to an increase in the level of catalase activity in erythrocytes (p≤0.01) with a simultaneous decrease in the concentration of MDA (p≤0.01) and restoration of the level of hydroperoxides in blood plasma (p≤0.05 and p≤0.01), which points to a pronounced antioxidant effect of melaxen in chronic mercury intoxication (2).

Correlation analysis revealed significant associations between the positive dynamics of haemostasiological parameters and the restoration of urine formation processes, as well as with the activity of LPO processes, in rats with preventive administration of melatonin. A significant correlation was established between the recovery of antithrombin activity and ELT with the recovery of tubular water reabsorption (p≤0.01 and -p≤0.05, respectively) and diuresis (p≤0.05 and p≤0.01, respectively). There was a positive correlation between changes in SFMCs parameters and the level of polyuria (P<0.05) and proteinuria (P≤0.01). A significant correlation between a decrease in MDA activity and a decrease in the concentration of protein in the urine (p≤0.01) and the concentration of soluble fibrin monomer complexes (p≤0.01) after two months of melatonin administration was also observed.

Thus, the results of the study are consistent with the previous reports suggesting the nephrotoxic effect of mercury, the activation of lipid peroxidation processes in mercury intoxication and the pronounced antioxidant properties of melatonin [7,8,9]. The study is first to demonstrate the role of melatonin in the mechanisms of prevention of toxic coagulopathy in chronic intoxication.

CONCLUSIONS

1. Intragastric administration of mercury chloride at a dose of 0.5 mg/kg causes a change in the parameters of vascular-platelet and coagulation haemostasis, the suppression of the activity of the anticoagulant blood system and fibrinolytic activity, and leads to the development of thrombinaemia. At the same time, disturbances in the haemostatic system are significantly associated with the disturbances in the processes of lipid peroxidation and urine formation.
2. Preventive administration of melatonin helps reduce the severity of pathological changes in the haemostatic system, while restoring the processes of urine formation, lipid peroxidation and the activity of antioxidant blood enzymes.
3. The results of the study suggest that melatonin administration can be recommended for further studies aimed at developing means for correcting haemostasis abnormalities associated with exposure to heavy metal compounds.

REFERENCES:

1. Petrishchev N.N. Papayan L.P. Hemostasis. Physiological mechanisms, principles of diagnosis of the main forms of hemorrhagic diseases. St. Petersburg; 1999. 120 p. (in Rus.)
2. Maseko P.B, van Rooy M., Taute H. Whole blood ultrastructural alterations by mercury, nickel and manganese alone and in combination: An ex vivo investigation // Toxicology and industrial health, 2021, 37(2), 98–111. https://doi.org/10.1177/0748233720983114
3. Wierzbicki, R., Prażanowski, M., Michalska, M., Krajewska, U. and Mielicki, W.P. Disorders in blood coagulation in humans occupationally exposed to mercuric vapors. J. Trace Elem. Exp. Med., 2002, 15, 21-29. https://doi.org/10.1002/jtra.1055
4. Momot A.P., Tsyvkina L.P., Taranenko I.A. Modern methods of recognition of thrombotic readiness, Barnaul, Altai. Univer., 2011, 138 p. (in Rus).
5. Raj D., Maiti S. Sources, Toxicity, and Remediation of Mercury: An Essence Review. Environ. Monit. Assess. 2019;191 https://doi.org/10.1007/s10661-019-7743-2
6. Kalaitzidis R.G., Duni A., Liapis G. Anticoagulant-related nephropathy: a case report and review of the literature of an increasingly recognized entity. Int Urol Nephrol. 2017; 49: 1401–7. https://doi.org/10.1007/s11255-017-1527-9
7. Raza Z, Naureen Z. Melatonin ameliorates the drug induced nephrotoxicity: Molecular insights. Nefrologia (Engl Ed). 2020;40(1):12-25. https://doi.org/10.1016/j.nefro.2019.06.009
8. Mitsiev A.K., Brin V.B., Mitsiev K.G. Melatonin prevention of nephrotoxic effects of mercury chloride in the experiment // Bulletin of new medical technologies. Electronic edition, no. 1, 2012, p. 56-67. (in Rus.)
9. Brin V.B., Buzoeva M.R., Gagloeva E.M. Prevention of manifestations of toxic nephropathy caused by heavy metals using zeolite-like clays Irlitov // Bulletin of new medical technologies. 2007. V. 14. No. 1. S. 196-198. (in Rus.)
10. Song YG. Effects of chronic mercury poisoning on blood coagulation and fibrinolysis systems.// Zhonghua laodong weisheng zhiyebing zazhi (Chinese journal of industrial hygiene and occupational diseases) vol. 2005, 23,6: 405-7.
11. Nielsen, V.G. Lethal concentrations of mercury or lead do not affect coagulation kinetics in human plasma // J Thromb Thrombolysis 2019, 48, 697–698.
12. Notariale, R., Infantino, R., Palazzo, E., & Manna, C. Erythrocytes as a Model for Heavy Metal-Related Vascular Dysfunction: The Protective Effect of Dietary Components. International journal of molecular sciences, 2021, 22(12), 6604. https://doi.org/10.3390/ijms22126604
13. Natochin Yu.V. Clearance of osmotically and sodium-free water: clinical implications / Nephrology, vol. 16, no. 2, 2012, pp. 9-15. (in Rus.)
14. Branco V, Caito S, Farina M, Teixeira da Rocha J, Aschner M, Carvalho C. Biomarkers of mercury toxicity: Past, present, and future trends. // J Toxicol Environ Health B Crit Rev. 2017;20(3):119-154. https://doi.org/10.1080/10937404.2017.1289834
15. Byshevskiĭ A.Sh., Galian S.L. Erythrocytes and leucocytes in realization of communication between lipid peroxidation and haemostasis // Biomed Khim. 2006;52(4):370-377. (in Rus.)

back