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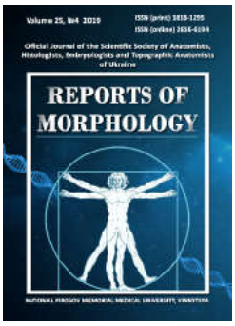

Evaluation of protective effect of Thiocetam drug by morphological changes in the heart and vessels after administration of lead nanoparticles of various sizes (experimental study)

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Introduction of nanotechnologies to the modern industry gave rise to new challenges. The issue of development and implementation of recommendations regarding the prevention of potential negative impact of lead nanoparticles on population health is of particular importance. The locally manufactured drug Thiocetam which possesses nootropic, antiischemic, antioxidative and membrane stabilizing properties has drawn our attention. The research aimed at studying the protective effect of Thiocetam in Wistar rats with simulated subchronic toxic effect of lead compounds of various sizes (by morphological changes in the heart and vessels). The experiments were conducted on Wistar rats (mean body weight of 160-180 g). Colloidal solutions of lead sulphide obtained by chemical synthesis with the use of sodium polyphosphate stabilizer, (PbS) with the mean size of 26-34 nm (1-PbS) and 50-80 nm (2-PbS), and lead nitrate $Pb(NO_3)_2$ (3-Pb) in the ionic form were used in simulating the toxic effect, while normal saline solution was administered to the control group. The studied substances were injected (intraperitoneally daily 5 times a week) in a dose of 0.94 mg/kg (in lead equivalent). The toxic effects were evaluated after 60 injections (three months) and one month after the discontinuation of exposure with and without Thiocetam. The drug Thiocetam in the dose of 250 mg/kg had been administered to rats intragastrically on an empty stomach daily for one month. Histological slides of the rats' myocardium and aortal wall were studied and morphometric analysis and statistical processing performed. In the postexposure recovery period period a lower degree of interstitial swelling and myocardial blood vessel filling was observed, which was considered to be a regression of damage. After the administration of Thiocetam a pronounced transverse striation of cardiomyocytes, the density of collagen fibers around cardiomyocytes and microvessels were revealed, which indicated the protective effect of pharmacological correction. However, leukocyte infiltration was also found in the myocardial or aortic microvessels in the experimental groups. Aortic morphometric data revealed no differences between the PbS NPs groups and $Pb(NO_3)_2$, although the aortic wall morphology was quite preserved. The use of Thiocetam prevented dystrophic changes in the atrial epicardium and the aortic adventitia, which indicate cytoprotective and connective tissue effects. In the postexposure period without pharmacological correction a tendency to spontaneous recovery of morphological changes of the heart and aortic walls under the influence of PbS NPs and lead nitrate was observed. However, morphometric parameters demonstrate the absence of complete recovery be it with or without Thiocetam.

Keywords: *lead, nanoparticles, morphological changes, aorta, myocardium, prevention of toxicities, Thiocetam.*

Introduction

The introduction of nanotechnology into modern production has opened wide prospects for technological development and significantly improves the consumer properties of products. In particular, synthesized nanocrystals of lead compounds, the so-called "quantum dots" 4-10 nm in size, have been successfully used in the

manufacturing of semiconductors, solar cells, biosensors, polymer composites, paints, electronic systems, including LEDs, and flat light emitting panels [8, 12, 19, 23, 29]. Today, the production and use of metal nanoparticles has become commercially available, which enables their penetration into the production areas and the environment and raises a number of questions about the potential risks of nanomaterials for human health [9, 11, 13, 27].

It is known that toxic effects of lead on human body are characterized by the presence of cardiovasotoxic, neurotoxic, hepatotoxic and nephrotoxic effects [3, 7, 20, 25, 26, 28]. In the current state of nanotechnology development researchers are faced with a new problem - the study of the effect of lead in the form of nanoparticles on the body, i.e. how the size of lead particles affects the body and is there any proportionality between their size and toxic effect [4, 15].

Of particular importance is the development and implementation of recommendations on preventing the potential negative impact of lead nanoparticles on population health. To date, a large number of pharmacological agents have been proposed for the purpose of clearing heavy metals from the body, reducing the manifestations of their toxic effects and increasing the general biological resistance of the body. The search for new drugs to prevent the development of intoxication is currently in progress [24].

For instance, the neuroprotective effect of Thiotriazoline, Mildronate and Magnesium B6 in mercury toxication was found [21, 22]; it was shown that under subchronic mercury exposure and combined pharmacological protection with Unithiol and Quercitin, myocardial structures restored due to the positive effect on the hemomicrocirculatory bed [10].

Experimental studies have shown high hepatoprotective efficacy of the drug Thiocetam in toxication with lead sulfide NPs: normalization of AST and ALT enzymes activity in blood serum was observed, as well as reduction of dystrophic changes in hepatocytes, normalization of blood filling of hemomicrocirculatory bed and structure of hepatic plates [2].

Our attention was also drawn to the locally manufactured drug Thiocetam which has nootropic, anti-ischemic, antioxidative and membrane-stabilizing properties.

The research aimed at studying the protective effect of Thiocetam in Wistar rats with simulated subchronic toxic effect of lead compounds of various sizes (by morphological changes in the heart and vessels).

Materials and methods

The experiments were conducted on Wistar rats (mean weight of 160-180 g). Animals were kept in the vivarium on a standardized diet with free access to drinking tap water. In simulating intoxication colloidal solutions of lead sulfide (PbS in sodium polyphosphate) with an average size of 26-34 nm (1-PbS) and 50-80 nm (2-PbS), and lead nitrate $Pb(NO_3)_2$ (3-Pb) in ionic form which is well soluble in water were used. The control group was injected with normal saline.

The studied substances were injected (intraperitoneally daily 5 times a week) (modelling of a working week) in a dose of 0.94 mg/kg (in lead equivalent). The toxic effects were evaluated after 60 injections (3 months) and one month after the discontinuation of exposure (postexposure recovery period - PEP).

Thus, 10 groups of animals were included into the study: 1 - control; 2 - (1-PbS); 3 - (2-PbS); 4 - (3-Pb); 5 - (1-PbS + Thiocetam); 6 - (2-PbS + Thiocetam); 7 - (3-Pb + Thiocetam); 8 - (1-PbS + PEP); 9 - (2-PbS + PEP); 10 - (3-Pb + PEP).

The drug Thiocetam had been administered to rats in the postexposure period (after 60 injections of the studied compounds of lead) daily on an empty stomach intragastrically at a dose of 250 mg/kg for 1 month. Thioacetam (manufactured by PJSC "Galichpharm" Lviv, Ukraine) is a fixed combination of Thiotriazoline (0.05 g in dry weight) and Piracetam (0.2 g).

The animals were withdrawn from the experiments by decapitation under mild ether anesthesia and their internal organs were harvested. All manipulations with animals were performed in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals, Used for Experimental and Other Scientific Purposes" (Strasbourg, 1985) and approved by the Bioethics Committee of the NAS of Ukraine.

The heart with aorta were fixed in 10% neutral formalin, dehydrated in isopropanol and embedded in paraffin (Leica Surgipath Paraplast Regular). Paraffin sections were made on a Thermo Microm HM 360 microtome. The sections were deparaffinized and stained with H&E following the picro-Mallory technique. The slides were studied using Olympus BX51 microscope. Morphometric analysis was performed using software Carl Zeiss (AxioVision SE64 Rel.4.9.1), magnification x200, x400.

Aorta wall thickness (mkm), adventitia of aorta thickness (mkm), comparative amount of collagen fibers in tunica adventitia (%), number of elastic membranes in tunica media (conventional units) were examined. The statistical study was performed in Origin Lab version 8.0 using the non-parametric Kruskal-Wallis test, because normal distribution of data was not proven. Data are presented as medians with smaller and larger quartiles (M [Q1-Q3]). The difference was considered statistically significant at $p<0.05$.

The studies were performed within the framework of research of State Institution "Kundiiev Institute of Occupational Health of the National Academy of Medical Sciences of Ukraine": "Comparative toxicity of micro- and nanoparticles of lead in experiments in vitro and in vivo (to the problem of improving the principles and methods of toxicological and hygienic studies of heavy metals)" (State registry number 0110U000299), "Investigation of the toxic effects of heavy metal nanoparticles, search and substantiation of preventive measures" (State registry

number 0116U000497) and Department of Histology and Embryology of Bogomolets National Medical University "Changes in internal organs and regulatory systems under conditions of experimental damage and historical aspects of the development of histology, cytology and embryology in Ukraine" (State registry number 0116U000121).

Results

Histological signs of toxic effect of lead on the heart have been studied. The increase in the interstitial space between the fibers of cardiomyocytes and their dystrophic changes in the atria were morphologically confirmed (in the ventricles there was only stasis of blood vessels) in the groups with PbS1 and PbS2. In the Pb3 group no dystrophic changes of the myocardium were detected, but in the atrial epicardium a focal accumulation of mast cells was found, which may indicate their infiltration/migration, and initiation of a proinflammatory response. In slides stained by the picro-Mallory technique for the detection of collagen fibers, a lower density of collagen around the arterioles and venules of the myocardium was found, which was considered to be a manifestation of the toxic effect of lead, and inhibition of the connective tissue elements morphogenesis. This was further indicated by the reduction in the number of cell nuclei in the wall of some myocardial vessels. In the aorta it was reflected by the decreased density of collagen fibers of the adventitia after 1-PbS and 2-PbS administration, impairment of the media (dissection, swelling, reduction of cell nuclei between the elastic membranes) (Fig. 1 A, B, C).

After Thiocetam administration cytological manifestations of the protective effect of pharmacological correction were revealed, such as a more pronounced transverse striation of cardiomyocytes, the density of collagen fibers around cardiomyocytes and microvessels. In group 1-PbS+Thiocetam local dystrophic changes of muscle fibers (loss of nuclei, acidophilia, loss of transverse striation, intercalated disks), focal accumulation of leukocytes in the ventricular epicardium were found.

Signs of stromal reorganization and increased fibroblast density were observed in the damage area. No differences in the morphofunctional changes of the myocardium in groups of different lead sizes (groups 2, 3, 5 and 6) were found. Infiltration of neutrophils, eosinophils, lymphocytes and macrophages around the aorta was also found in aorta of 1-PbS+Thiocetam and 2-PbS+Thiocetam groups. No pronounced structural disturbances were observed in the 3-PbS+Thiocetam, but by all morphometric

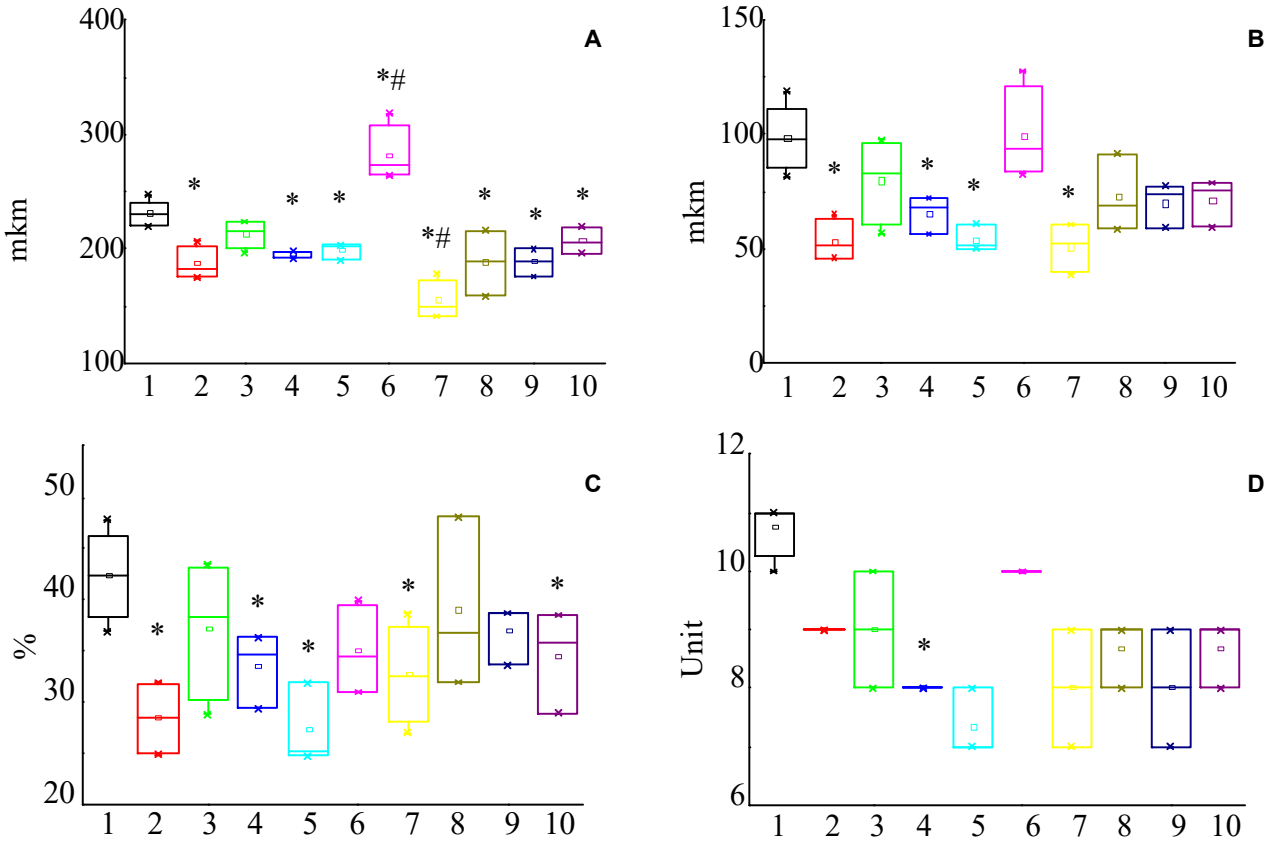

Fig. 1. Results of the aorta wall morphometry (M [Q1-Q3]). Note: A - aorta wall thickness; B - t. adv. thickness; C - relative amount of t. adv. in the aorta; D - number of elastic membranes in t. media; * - significant difference to control ($p<0.05$); # - significant difference to PEP period without Thiocetam ($p<0.05$).

indicators the wall thickness was less than the control values. The structural organization of the adventitia did not differ significantly in the comparison groups.

In the PEP period there was a lower degree of interstitial swelling and moderate blood filling of the myocardial vessels, with the accumulation of leukocytes in single ventricular capillaries detected in the 1-PbS+PEP group. Histological changes of the aortic wall were also reflected in the reduction of its thickness, however, no morphological signs of the media impairment, and the density of elastic membranes were observed. According to the results of morphometric evaluation no statistically significant difference between groups of subchronic experiment (groups 2, 3, 4) and PEP period (groups 8, 9, 10) was found, this was also the case with comparator Thiocetam groups.

The results of the studies indicate that administration of Thiocetam had a partial protective effect, but this was not reflected in the morphometric parameters.

Discussion

The task of this experimental study was to investigate the cardio- and vasotoxic effects of lead compounds and the possibility of their correction by Thiocetam. As described above, inhaled administration of the lead sulfide NPs to the body of experimental animals caused inflammatory changes in the lungs, which were accompanied by the development of oxidative stress and decreased activity of antioxidant enzymes. Moreover, the toxicity of PbS NPs was closely related to their size [14]. Prolonged intraperitoneal administration of lead sulfide NPs revealed their hepatotoxic effect with impaired protein metabolism [1, 16, 18]. In vivo experiments have shown high neurotoxicity of lead sulfide NPs and demonstrated the pathogenetic role of calcium homeostasis disorders; also found was significant reproductive toxicity of lead compounds in nanoforms [5, 6]. To date, there are only few works on the toxic effect of lead NPs on the cardiovascular system and there is virtually no data on their long-term effects.

The results of our own studies lead to the conclusion that PbS NPs have cardiotoxic effects and negatively affect myocardial microcirculation. Morphological signs of cytotoxic action in the myocardium include decreased density of the cardiomyocytes cytoplasm, loss of transverse striation which is more pronounced in the inner layers of the myocardium muscle fibers, with the outer layers being more compact. In this case no pronounced difference in toxic effect between lead nanoparticles of 26-34 nm (1-PbS) and 50-80 nm (2-PbS) was detected, except for single areas of necrosis after administration of 2-PbS. There were no specific differences in structural changes of the aorta wall when exposed to lead nanoparticles of different sizes. The main morphological manifestation of the disorders is the reduction of connective tissue content in adventitia in the NP 1-PbS, 2-PbS and disorganization of the elastic membranes of the media caused by the interstitial swelling, which result in a statistically significantly smaller aortic wall thickness by 14.3 %. However, no statistically significant difference was observed between the effects of PbS NPs and lead nitrate $Pb(NO_3)_2$.

Analysis of the effect of Thiocetam on the development of toxic damage to the heart and aorta showed cytoprotective effects in exposure to lead nitrate. The morphological structure of the aortic wall was more preserved despite its smaller thickness, whereas after the introduction of 2-PbS an increase in the thickness of the aorta was observed due to structural disorders, dissection of elastic membranes of t.media fibers in particular. Increased fibroblast density in t.adventitia in the NPs 1-PbS, 2-PbS and lead nitrate groups was considered to be a protective effect on aortic connective tissue morphogenesis. The effect of Thiocetam can be explained by its effect on the processes of peroxidation, the antioxidant system, especially superoxide dismutase, which reduces the cytotoxic effect of lead in vitro and in vivo [17].

Conclusions

The use of Thiocetam prevented dystrophic changes in the atrial epicardium and the adventitia of the aorta, indicating cytoprotective effect and influence on the connective tissue. In the post-exposure period without pharmacological correction, a tendency to spontaneous recovery of morphological changes of the heart and aortic walls under the influence of PbS NPs and lead nitrate was detected. However, as evidenced by morphometric parameters complete recovery does not occur neither with nor without Tiocetam.

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ОЦІНКА ПРОТЕКТОРНОЇ ДІЇ ПРЕПАРАТУ "ТІОЦЕТАМ" ЗА МОРФОЛОГІЧНИМИ ЗМІНАМИ В СЕРЦІ ТА СУДИНАХ ПРИ ВВЕДЕННІ НАНОЧАСТИНОК СВИНЦЮ РІЗНИХ РОЗМІРІВ (ЕКСПЕРИМЕНТАЛЬНЕ ДОСЛІДЖЕННЯ)

Губар І.В., Сокуренко Л.М., Савосько С.І., Апихтіна О.Л., Яворовський О.П., Чайковський Ю.Б.

Впровадження нанотехнологій в сучасне виробництво призвело до нових викликів. Особливо важливим є питання розробки та впровадження в практику рекомендацій щодо попередження можливого негативного впливу наночасток свинцю на здоров'я населення. Нашу увагу привернув вітчизняний фармакологічний препарат "Тіоцетам", котрий має ноотропні, протиішемічні, антиоксидантні та мембраностабілізуючі властивості. Метою дослідження було вивчення протекторної дії фармакологічного препарату "Тіоцетам" при моделюванні у щурів лінії Вістар субхронічної інтоксикації сполуками свинцю різного розміру (за морфологічними змінами в серці та судинах). Експерименти проведено на щурах лінії Wistar (середня вага 160-180 г). При моделюванні інтоксикації були використані колоїдні розчини сульфіду свинцю, отримані методом хімічного синтезу, з використанням стабілізатора поліфосфату натрію, (PbS) з середнім розміром 26-34 нм (1-PbS) і 50-80 нм (2-PbS), та в іонній формі - нітрат свинцю $Pb(NO_3)_2$ (Pb3). Контрольній групі вводили фізіологічний розчин. Досліджувані речовини вводили внутрішньоочеревинно щоденно 5 разів на тиждень у дозі 0,94 мг/кг (у перерахунку на свинець). Токсичні

ефекти оцінювали після 60 введень (3 місяці) та через 1 місяць після припинення експозиції. Препарат "Тіоцетам" вводили щурам у постекспозиційному періоді щоденно натще внутрішньошлунково у дозі 250 мг/кг протягом 1 місяця. Вивчали гістологічні зрізи міокарда щурів та стінки аорти з наступним морфометричним аналізом та статистичною обробкою. У постекспозиційному відновлювальному періоді відмічено менший ступінь інтерстиційного набряку і кровонаповнення судин міокарда, що оцінено як регрес ушкодження. Після введення "Тіоцетаму" виявлено виражену поперечну посмугованість кардіоміоцитів, щільність колагенових волокон навколо кардіоміоцитів і мікросудин, що вказувало на захисний вплив фармакокорекції. Але у мікросудинах міокарда або аорти в експериментальних групах встановлено інфільтрацію лейкоцитів, також не виявлено різниці за морфометричними даними аорти між групами PbS NPs і $Pb(NO_3)_2$, хоча морфологія стінки аорти була досить збереженою. Застосування "Тіоцетаму" запобігало дистрофічним змінам у епікарді передсердь та адвентиційній оболонці аорти, що свідчить про цитопротекторну дію і вплив щодо сполучної тканини. У постекспозиційному періоді без фармакологічної корекції виявлено тенденцію до спонтанного відновлення морфологічних змін стінок серця та аорти під впливом PbS NPs і нітрату свинцю. Однак повноцінного відновлення ні при застосуванні "Тіоцетаму", ні без нього, не відбувається, про що свідчать морфометричні показники.

Ключові слова: *свинець, наночастинки, морфологічні зміни, аорта, міокард, профілактика інтоксикації, "Тіоцетам".*

ОЦЕНКА ПРОТЕКТОРНОГО ДЕЙСТВИЯ ПРЕПАРАТА "ТИОЦЕТАМ" ПО МОРФОЛОГИЧЕСКИМ ИЗМЕНЕНИЯМ В СЕРДЦЕ И СОСУДАХ ПРИ ВВЕДЕНИИ НАНОЧАСТИЦ СВИНЦА РАЗЛИЧНЫХ РАЗМЕРОВ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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Внедрение нанотехнологий в современное производство привело к новым вызовам. Особенно важным является вопрос разработки и внедрения в практику рекомендаций по предупреждению возможного негативного влияния наночастиц свинца на здоровье населения. Наше внимание привлек отечественный фармакологический препарат "Тиоцетам", который имеет ноотропные, противоишемические, антиоксидантные и мембраностабилизирующие свойства. Целью исследования было изучение протекторного действия фармакологического препарата "Тиоцетам" при моделировании у крыс линии Вистар субхронической интоксикации соединениями свинца разного размера (по морфологическим изменениям в сердце и сосудах). Эксперименты проведены на крысах линии Wistar (средний вес 160-180 г). При моделировании интоксикации были использованы коллоидные растворы сульфида свинца, полученные методом химического синтеза с использованием стабилизатора полифосфата натрия, (PbS) со средним размером 26-34 нм (1-PbS) и 50-80 нм (2-PbS), и в ионной форме - нитрат свинца $Pb(NO_3)_2$ (Pb3). Контрольной группе вводили физиологический раствор. Исследуемые вещества вводили внутрибрюшинно ежедневно 5 раз в неделю в дозе 0,94 мг/кг (в пересчете на свинец). Токсические эффекты оценивали после 60 введений (3 месяца) и через 1 месяц после прекращения экспозиции. Препарат "Тиоцетам" вводили крысам в постэкспозиционном периоде ежедневно натощак внутрижелудочно в дозе 250 мг/кг в течение 1 месяца. Изучали гистологические срезы миокарда крыс и стенки аорты с последующим морфометрическим анализом и статистической обработкой. В постэкспозиционном восстановительном периоде отмечены меньшая степень интерстициального отека и кровенаполнения сосудов миокарда, что оценено как регресс повреждения. После введения "Тиоцетама" выявлено выраженную поперечную исчерченность кардиомиоцитов, плотность коллагеновых волокон вокруг кардиомиоцитов и микрососудов, что указывало на защитное влияние фармакокоррекции. Но в микрососудах миокарда или аорты в экспериментальных группах установлено инфильтрацию лейкоцитов, также не выявлено разницы по морфометрическими данным аорты между группами PbS NPs и $Pb(NO_3)_2$, хотя морфология стенки аорты была достаточно сохранной. Применение "Тиоцетама" предотвращало дистрофические изменения в эпикарде предсердий и адвентициальной оболочке аорты, что свидетельствует о цитопротекторном действии и влиянии на соединительную ткань. В постэкспозиционном периоде без фармакологической коррекции выявлена тенденция к спонтанному восстановлению морфологических изменений стенок сердца и аорты под влиянием PbS NPs и нитрата свинца. Однако полноценного восстановления ни при применении "Тиоцетама", ни без него, не происходит, о чем свидетельствуют морфометрические показатели.

Ключевые слова: *свинец, наночастицы, морфологические изменения, аорта, миокард, профилактика интоксикации, "Тиоцетам".*