

POSITIVE EFFECT OF ENTEROSORPTION IN DOXORUBICIN-INDUCED CARDIOHEMODYNAMICS ALTERATION

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Background. Anthracycline antibiotics are one of the most effective anti-cancer drugs, but their cardiotoxicity what limits its therapeutic use.

Objective. To analyze the efficiency of enterosorption in doxorubicin-induced cardiohemodynamics violation.

Methods. Subchronic doxorubicin toxicity was modeled by injecting the anthracycline antibiotic intraperitoneally at a dose of 5 mg/kg once a week for 4 weeks, in total 20 mg/kg. Male Wistar rats were randomly distributed into 3 groups: control; DOX-group and DOX + enterosorbent C2 rats ($\gamma=0.18 \text{ g/cm}^3$, BET area $2162 \text{ m}^2/\text{g}$). Cardiohemodynamics was studied by the Millar Instruments, heart morphometry – by Avtandilov's method.

Results. Mortality rate in DOX-group was 25%. Ejection fraction and Stroke work indices were lower compared to the control group, preload adjusted maximal power decreased by 57.6%, minimum volume and end-systolic volume increased by 76,2 and 67.5% respectively. End-systolic stiffness of left ventricle (E_{\max}) as well as arterial elastance (E_a) and end-systolic pressure had tended to decrease. Indices of left ventricle (LV) volume at systole increased: $V@dPdt_{\max}$ – by 73.3%, $V@dPdt_{\min}$ – by 81.9%. End-diastolic volume increased by 54.6%. As for the $dPdt_{\text{mir}}$ and Tau constant we observed the slight tendency to its decline. Endocardial surface of LV increased by 42.7%, Planimetric Index – by 40.4% compared to the control group of rats.

In DOX+C2 group mortality rate was 18.75%. We observed the strong tendency to normalization of the main indices compared to the DOX group and shrinking of the LV. We want to underline the positive trends especially in Ejection Fraction (from $39.62 \pm 10.50\%$ to $46.23 \pm 11.46\%$) and Stroke Work (from 6406.50 ± 3345.83 to $10363.14 \pm 7329.55 \text{ mmHg} \times \text{uL}$) as important indicators of the effectiveness of cardiac pump function.

Conclusions. Enterosorption demonstrated positive impact on the doxorubicin-induced violated cardiohemodynamics and decreased the mortality rate. It is a ground for further investigations.

KEY WORDS: doxorubicin-induced subchronic toxicity; heart damage; enterosorption; cardiohemodynamics parameters.

Introduction

Anthracycline antibiotics are widely used to treat many types of malignancies because of their high efficacy. But, also, they are cardiotoxic, what limits their therapeutic use and cumulative dose [1,2]. Doxorubicin (Adriamycin, a derivative of rubomycin – 14-hydrorubomycin) is a part of chemotherapy schemes for treatment of breast and prostate cancer, solid tumors in children, sarcomas, and others. Multiple mechanisms of heart damage by anthracyclines are recognized. Oxidative stress and generation of reactive oxygen species (ROS) by “anthracycline-iron”

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complex; cardiac muscle's accumulation of highly reactive alcoholic metabolite doxorubicinol (DOXol); cytokines disturbances; as a consequence of endogenous intoxication and bacterial translocation because of mucositis – are only a few possible ways of cardiomyocytes injury [3–7].

Till today there are no definite and 100% efficient methods for prevention and treatment of anthracyclines-induced cardiotoxicity. Iron-chelating agent dexrazoxane was implemented into protocols based on its capability to prevent free radical release [8,9]. But there are some facts that this agent could decrease the efficacy of anti-cancer chemotherapy [10]. That is why the search of effective means to ameliorate the cardiotoxicity of anthracyclines, which do not

attenuate the anti-tumor activity of drugs, remains actual. Sorption Detoxification is a well-known method for cleaning of body fluids from toxic endogenous or exogenous compounds. The most widely used types of this method are the purification of blood or its components (hemisorption), oral administration of sorption materials (enterosorption), and application-sorption therapy of wounds and burns [11]. Our previous studies with enterosorbents Carboline and carbon granular oral adsorbent C2 demonstrated promising results to alleviate the side effects caused by cytostatic agents melphalan and cisplatin (bone marrow suppression, gastrointestinal toxicity, testes damage, etc.) [12–15]. Enterosorbent C2, which has optimized and shifted to mesopores porous structure, in combination with an official biosimilar of granulocyte colony-stimulating factor (filgrastim) ameliorated hematologic toxicity and oxidative stress indexes much better than each of these preparations alone [16].

The objective of this study is the assessment of the capability of carbon granular oral adsorbent C2 to diminish the doxorubicin-induced heart damage.

Methods

Materials

Doxorubicin hydrochloride (Doxorubicin Teva 10 mg/5ml, concentrate for solution for infusion, TEVA Pharmachemie, the Netherlands) was used for experiments. Carbon oral adsorbent C2 was specially designed at the Department of Means and Methods of Sorption Therapy of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology (IEPOR). Parameters of enterosorbent C2 are next: bulk density $\gamma=0.18 \text{ g/cm}^3$, granules with a diameter of 0.15–0.25 mm, the porous structure of C2 is well developed and shifted toward mesopores, which surface is $565 \text{ m}^2/\text{g}$. BET (Brunauer-Emmett-Teller) surface area is $2162 \text{ m}^2/\text{g}$.

Animal studies

All experiments were carried out with male Wistar rats, 180–220 g of primary weight, which were reared at TNMU animal facility (Ternopil, Ukraine). All procedures were done according to the local bioethical committee guidelines which conform to the rules and requirements of European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986) and EU Directive on the Use of Animals for Research Directive 2010/63/EU. A common light-dark cycle was maintained for rats and fed on common rodent

chow diet with tap water *ad libitum*, according to the guidelines for animal care.

A well-documented regimen was used for the induction of heart damage by doxorubicin [17]. Animals were randomly assigned to 3 groups: 1) control group (n=7); 2) rats treated with DOX (DOX-group) (n=16); 3) rats treated with both DOX and carbon enterosorbent C2 (DOX+C2) (n=16).

Subchronic doxorubicin toxicity was modeled by injecting the anthracycline antibiotic intraperitoneally at a dose of 5 mg/kg once a week for 4 weeks, in total 20 mg/kg [17]. The animals serving as control received the same volume of saline intraperitoneally once a week for a total of 4 weeks. Newly designed carbon oral adsorbent C2 was given into the stomach via a custom rigid tube once a day at a dose of 5 ml per kg (or 1 ml for each 200 g of rat body weight; or 900 mg of the dry mass of the enterosorbent). We started enteral sorption therapy the next day after the first injection of Doxorubicin. The sorbent was given as a suspension in an appropriate volume of distilled water. The rats of the control group received an equal volume of distilled water. On the days of doxorubicin injection and one day before it, the enterosorbent was not given to avoid any pharmacokinetics disruption.

Cardiohemodynamics measurements

For the direct cardiac function evaluation, we used Millar pressure-volume (P-V) system (MPVS-300, Millar Instruments, Houston, TX, USA). On the 29th day of the experiment counting from the first injection of doxorubicin, under urethane general anesthesia (1.5 g/kg) the right carotid artery was exposed and ligated distally, the artery was clamped and incised, and a 0.5 cm long 90 PE tube was inserted as a catheter guide. A 2-Fr Mikro-Tip catheter (SPR-838, Millar Instruments, Houston, TX, USA) was advanced through the guide into the LV under pressure control; a ligature was then tightened around the catheter to avoid blood loss [18]. After stabilization for 5 min, signals were continuously sampled at a sampling rate of 1000 samples/sec by the MPVS-300 system, recorded, and displayed on a personal computer by the PowerLab System and ChartTM v.5.4.2 software (ADInstruments, Millar Instruments) for 15–20 min.

The relation of pressure and volume of the left ventricle was performed by software PVAN 3.6 (AD Instruments, Millar Instruments) with the conversion of relative volume units (RVU) into absolute one (equation slope $20,25 \times \text{RVU} -$

intercept 29,05). The Millar P-V System simultaneously and continuously measures left ventricle (LV) pressure (P) and volume (V) from the beating heart, producing characteristic PV loops readings of which a variety of cardiovascular parameters, such as heart rate (HR), cardiac output (CO), stroke volume (SV), ejection fraction (EF), stroke work (SW), dP/dt_{max} and dP/dt_{min} are derived. End-systolic pressure (ESP), end-systolic volume (ESV), end-diastolic pressure (EDP), end-diastolic volume (EDV), stroke volume (SV), stroke work (SW), maximum dP/dt ($dPdt_{max}$), minimum dP/dt ($dPdt_{min}$), tau, maximum dV/dt ($dVdt_{max}$), minimum dV/dt ($dVdt_{min}$), maximum pressure (P_{max}), minimum pressure (P_{min}), maximum volume (V_{max}), and minimum volume (V_{min}) were also analyzed.

Morphometrics of the heart

To estimate chronic changes of the shape and size, the hearts of the rats were used for measuring and evaluating of the planimetric index. For indirect planimetry of the endocardial surface of the rats' hearts, ventricles were taken accordingly to Avtandilov G.G. method [19] in Esypova I.K. et al. modification [20]. We measured the endocardial surfaces of the left (E_{LV}) and right ventriculi's wall area (E_{RV}). Planimetric index (PI) was calculated as:

$$PI = E_{LV} \div E_{RV}$$

where E_{LV} is the endocardial surfaces of the left ventricle wall area and E_{RV} is the endocardial surfaces of the right ventricle wall area.

Statistical analysis

The normality of data distribution was tested using Kolmogorov-Smirnov test, homogeneity of variance - Levene's test. Mann-Whitney test and One-way ANOVA was applied to test the differences between the groups. Statistical analysis was performed using Microsoft Excel XP (USA) and Statistica 10.0 (StatSoft Inc., USA). Differences were considered significant if the probability of Type I error was less than 0.05. $P < 0.05$ was considered significant.

Results

In DOX-group the number of prematurely deceased rats was four, in DOX+C2 group - three rats died before the end of the experiment. All abovementioned animals died after the 4th injection of doxorubicin during the last week of the experiment. Among survived rats we observed typical clinical signs of heart failure: rats showed clear signs of dyspnea, from mild to severe ascites, different stages of hydrothorax and liver enlargement; their common activities were reduced compared to the rats of the

control group. Those rats had less intensity compared to the untreated group of animals.

The pump function of the heart was analyzed by next parameters: ejection fraction, stroke volume and stroke work and cardiac output, as well as maximal power and preload adjusted maximal power (PaMP) (table 1). These parameters are load-dependent and consequently represent poor contractility indices. Increased cardiac output, high heart rate as well as stroke volume are the typical signs of cardiac dysfunction and followed systemic hemodynamic changes and our results supposed it. It was a strong tendency for increasing of the all abovementioned indices, but enteral sorption therapy partly disrupts it. Ejection fraction in DOX-group rats was lower, but in the group DOX+C2, we see the tendency to its normalization. The same tendency was for the stroke work: from 6406.50 ± 3345.83 in rats, which received injections of doxorubicin, it increased to 10363.14 ± 7329.55 mmHg \times uL for rats which got oral adsorbent concomitantly. While the index in rats of the control group was 7036.43 ± 5036.46 mmHg \times uL.

Minimum volume increased by 76,2%, end-systolic volume - by 67.5%. For both indices, we observed the tendency for decreasing by oral adsorbent therapy, but they did not come close to the numbers of control group rats.

In the rats of DOX-group the index of maximal power did not change significantly, but the strong tendency to its decreasing we saw, while preload adjusted maximal power (PaMP) was lower by 57.6% compared to the control group. Enteral sorption therapy promoted the tendency to normalization of the indices. End-systolic stiffness of left ventricle (E_{max}) had a strong tendency to decreasing from 4.55 ± 2.93 to 2.74 ± 2.02 (what means that left ventricle was dilated and lost end-systolic elastance), while carbon oral adsorbent C2 increased this index to 5.30 ± 0.44 .

Specific parameters as the volume at the point of maximal speed of pressure change ($V@dPdt_{max}$) and volume at the point of maximal speed of pressure decline ($V@dPdt_{min}$) are used for assessment of LV volume at systole. So, $V@dPdt_{max}$ increased by 73.3%, while $V@dPdt_{min}$ - by 81.9%.

During diastole, the myocardium stops shortening and generating force and relaxes. Diastolic function was analyzed by changes of end-diastolic pressure and volume, the peak rate of pressure decline ($dPdt_{min}$) - isovolumic relaxation, constant Tau by Weiss method (τ_w).

Table 1. Cardio-hemodynamics indices in rats, which received doxorubicin and enteral sorption therapy with oral carbon adsorbent C2.

Index	Control group	DOX group	DOX + C2 group
HR (min ⁻¹) heart rate	321.0±43.89	356.64±48.82	378.38±33.86
Maximum Volume (uL)	146.79±13.08	232.76±76.58	236.68±102.07
Minimum Volume (uL)	78.27±15.17	137.93±46.96*	126.05±35.68
End-systolic Volume (uL)	84.87±17.73	142.16±47.56*	130.76±36.68
End-diastolic Volume (uL)	142.56±11.36	220.44±70.94*	223.75±85.04
Maximum Pressure (mmHg)	116.24±21.53	102.0±22.51	111.85±14.35
Minimum Pressure (mmHg)	4.97±3.89	4.15±3.39	2.10±1.65
End-systolic Pressure (mmHg)	109.57±25.12	96.22±24.07	104.58±16.72
End-diastolic Pressure (mmHg)	9.10±4.28	6.72±4.54	5.99±3.77
Stroke Volume (uL)	68.52±21.34	94.835±39.90	120.88±78.45
Ejection Fraction (%)	46.15±11.83	39.62±10.50	46.23±11.46
Cardiac Output (uL/min)	2222.85±8424.99	33103.55±13814.04	44721.45±28511.89
Stroke Work (mmHg×uL)	7036.43±5036.46	6406.50±3345.83	10363.14±7329.55
Arterial Elastance (Ea), (mmHg/uL)	2.25±0.71	1.06±0.49	1.11±0.56
dPdt max (mmHg/sec)	11758.0±5232.28	9897.43±3142.76	12769.50±2861.17
dPdt min (mmHg/sec)	-7312.86±2477.79	-7062.50±1742.62	-8928.12±3274.57
dVdt max (uL/sec)	2811.14±1048.07	4783.57±1703.76	4489.87±2985.50
dVdt min (uL/sec)	-3345.57±1283.04	-3893.5±1345.52	-4751.13±2491.48
P@dVdt max (mmHg)	38.27±32.11	40.16±35.79	34.62±36.27
P@dPdt min (mmHg)	88.67±50.41	64.69±13.78	74.00±21.68
V@dPdt max (uL)	124.90±25.62	216.46±76.45*	228.02±102.85*
V@dPdt min (uL)	79.91±15.49	145.33±52.64*	129.76±36.71
Tau(W) (msec)	12.69±5.87	11.41±5.01	9.25±1.96
Tau(G) (msec)	18.34±11.18	13.80±5.68	11.90±3.39
Maximal Power (mWatts)	43.89±34.61	38.94±18.71	57.61±32.30
Preload adjusted maximal power, PaMP (mWatts/μL ²)	20.81±15.88	8.82±4.78*	12.38±5.77
E _{max}	4.55± 2.93	2.74±2.02	5.30±0.44

Notes. The data are expressed as means (M) ± standard deviation (SD); * - p<0,05 comparing to control group; dPdt_{max} - peak rate of pressure rise; dPdt_{min} - peak rate of pressure decline; dVdt_{max} - peak rate of volume rise; dVdt_{min} - peak rate of volume decline; P@dVdt_{max} - Pressure at dV/dt max; P@dPdt_{min} - Pressure at dP/dt_{min}; V@dPdt_{max} - Volume at dP/dt_{max}; V@dPdt_{min} - Volume at dP/dt_{min}; Tau (G) - relaxation time constant calculated by Glantz method (regression of dP/dt versus pressure); Tau (W) - relaxation time constant calculated by Weiss method (regression of log(pressure)); E_{max} - end-systolic elastance.

End-diastolic volume increased by 54.6% in the group of rats, which received doxorubicin compared to the control rats. As for the dPdt_{min}, we observed a slight tendency to its decline, as well as for the Tau constant.

After 4 injections of Doxorubicin on 29th day of the experiment, the endocardial surface of

the left ventricular wall area increased by 42.7% (p<0.001) compared to control group of rats (table 2). At the same time, there were no changes in the right ventricular wall area. In rats which received enterosorption together with doxorubicin, the endocardial surface of the left ventricular wall area index decreased

Table 2. The influence of enterosorption on morphometric indexes of the heart ventricles in subchronic doxorubicin toxicity in rats.

Index	Control group	DOX-group	DOX+C2 group
The endocardial surface of left ventricular wall area, mm ²	118.0±4.45	168.4±7.63*	132.6±3.06* **
The endocardial surface of right ventricular wall area, mm ²	132.2±6.27	134.8±6.54	137.8±4.88
Planimetric index (PI)	0.894±0.010	1.25±0.032*	0.965±0.022**

Notes: The data are expressed as means (M) ± standard error (SE). p<0.05 compared to * - control group; ** - DOX-group.

by 21.3% compared to the DOX group, but it was still larger than in rats of the control group.

Doxorubicin injections increased the Planimetric index (PI) the by 40.4% compared to the control group (from 0.89 ± 0.01 to 1.25 ± 0.03), while in DOX+C2 group it decreased by 22.8% (0.96 ± 0.02 , $p < 0.001$).

Discussion

Our study deals with the effect of enterosorption on doxorubicin-associated cardiac toxicity. Doxorubicin's use in patients is limited by its cardiac toxicity. Today a new subspecialty appeared – cardio-oncology, which focuses on prevention, detection, monitoring, and treatment of cardiovascular pathology during anti-cancer chemotherapy [21]. It is a marker of the high importance of this problem because long term survival of childhood cancers is more than 70% for now [6] and continued to increase [22]. Strong links between cancer and heart disease are recognized, that is why a clinical need for optimized cardio-oncology patient management is growing. Among anti-cancer agents, the most capable drugs to cause the dilative cardiomyopathy are anthracyclines and cyclophosphamide [16,23]. Dose-dependent irreversible heart damage occurs in 1.7% of patients mostly via oxidative stress activation and by inhibition of transcriptions of genes, which are responsible for the synthesis of the contractile proteins [3,16]. Up to 3% of heart transplantations were done for patients because of doxorubicin therapy [6]. It is known that the prognosis of patients who develop doxorubicin-induced congestive heart failure is poor: approximately ~50% mortality in 1 year [3]. Monoclonal antibody trastuzumab and low molecular tyrosine kinase inhibitors as sunitinib and sorafenib may cause heart damage too [23]. They modulate mitochondrial integrity, deplete ATP and lead to contractile dysfunction. But in this case, the contractile function of the left ventricle improves after drugs discontinuation [23].

We used typical widespread modeling to induce congestive heart failure in rats: four injections of DOX at the dose of 5 mg/kg for cumulative dose 20 mg/kg and got the cardiohemodynamic disruption [17]. So, this model could be used for assessment of the capability of different substances and drugs to impact the heart systolic and diastolic function. One of the experimental morphometric methods to measure and estimate the type and deepness of heart injury is weighing and weight measurement of different parts of the organ namely

left and right ventricle with the septum (ventricle index, Fulton index, etc.). The planimetric method allows estimating changes of both ventricles by measuring the endocardial surfaces area [19]. And this method is validated to estimate the chronic changes of the heart morphology, while cardiohemodynamics violations measured by Millar Instruments are quite good for assessment of acute functional changes in heart work.

A wide variety of indexes that can be quantified by analyzing pressure-volume (PV) loops have been proposed to characterize the left ventricle systolic and diastolic performance. In the present study, doxorubicin-associated cardiac dysfunction was manifested by a reduction in cardiac systolic and diastolic hemodynamic function. We have shown statistically significant differences between DOX and control groups in parameters of end-systolic and end-diastolic volumes as well as volumes at the point of maximal speed of pressure change and pressure decrease. Also, we have shown a 57.6% decrease in Preload adjusted maximal power. Doxorubicin at the cumulative dose of 20 mg per kg promoted the heart dilation, which was confirmed by increased indices of the endocardial surface of the left ventricular wall area and planimetric index. Our previous study demonstrated the decreased mass of the heart in subchronic doxorubicin toxicity. So, despite only the slight tendency of ejection fraction declining, these important changes already indicate the onset of the dilated cardiomyopathy. Such results are supported by research on the male New Zealand white rabbits with doxorubicin-induced heart damage [24]. So, we may conclude, that early myocardial effects of doxorubicin-induced cardiotoxicity are presented. We may talk about early stages of dilated cardiomyopathy with still preserved ejection fraction, but with clinical signs of congestion in survived rats – non-failing dilated left ventricle in survived animals. Our results are confirmed by the study of Lodi M. et al. [25]: A significantly reduced ejection fraction was seen on day 80 only. They modeled cardiomyopathy by 6 IV injection of DOX at the dose of 1.5 mg/kg on the 8th, 11th, 14th, 17th, 20th and 23rd days of the experiment [25]. Also, the results of our histological examination of heart tissues presented revealed loss of myofibrils and striations, as well as cytoplasmic edema.

Our previous study demonstrated that enterosorption with C2 ameliorates the morphological signs of heart damage [26]. Also, we

observed improvements of hematological parameters, kidney's function and decrease of endogenous intoxication markers. Those data are in press.

It is important to mention that the concomitant course of enterosorption during this experiment decreased the mortality rate. In rats which received doxorubicin, it was 25% (4 rats from 16), while at the DOX+C2 group – 18.75% (3 rats from 16).

DOX+C2 rats' group has shown a statistically significant difference compared to the control group in the parameter of volume at the point of maximal speed of pressure change. $V@dPdt_{max}$ increased by 82.6%.

All 26 parameters of cardiohemodynamics were altered in rats which received doxorubicin at the total dose of 20 mg/kg. More than a half (14 parameters) among them demonstrated tendency to normalization under the influence of enteral sorption therapy. Especially we want to notice the positive tendency in indices of Preload adjusted maximal power, PaMP (from 8.82 ± 4.78 to 12.38 ± 5.77 mWatts/ μL^2), Maximal Power (from 38.94 ± 18.71 to 57.61 ± 32.30 mWatts, and it was even higher than in the control group – 43.89 ± 34.61 mWatts), Stroke Work (from 6406.50 ± 3345.83 to 10363.14 ± 7329.55 mmHg \times uL, while the control group index was 7036.43 ± 5036.46 mmHg \times uL) and Ejection Fraction from $39.62 \pm 10.50\%$ to $46.23 \pm 11.46\%$, when in the control group it was $46.15 \pm 11.83\%$).

Conclusions

Doxorubicin at the total dose of 20 mg/kg caused pronounced violation of cardiohemodynamics. Systolic indices as Ejection fraction, stroke work, end-systolic elastance (E_{max}), end-systolic pressure – all these indices demonstrated a tendency to decline, preload adjusted maximal power (PaMP) was lower by 57.6% compared to the control group. It is a marker of weaker pump function and poor contractility of the heart. Morphometry showed dilation of the left ventricle and increased planimetric index. At the same time, the diastolic indices were disrupted too. End-diastolic volume significantly increased by 54.6%, the index of peak rate of pressure had a tendency for declining, as well as Tau(w). The indices of volume at the point

of maximal speed of pressure change ($V@dPdt_{max}$) and volume at the point of maximal speed of pressure decline ($V@dPdt_{min}$) significantly increased in rats, which received doxorubicin. It confirms the diastolic dysfunction presence.

Enteral sorption therapy mostly normalized and improved violated indices and decreased the rate mortality of rats. We observed shrinking of the endocardial surface of the left ventricular wall area by 21.3% and decreasing of Planimetric Index. Those results demonstrate that enterosorption could prevent remodeling of the heart chambers. Our cardiohemodynamics investigations included more than 20 parameters and though mostly they are not statistically significant we want to underline the positive trends in DOX+C2 rats comparing to DOX-group, especially in Ejection Fraction and Stroke Work parameters as they are the important indicators of the effectiveness of cardiac pump function. Such results could be explained by the fact that measurement of hemodynamics was done one week later after the last 4th injection of doxorubicin, and we observed the consequences of mechanisms of adaptation in survived rats.

Our research demonstrated promising results of the efficiency of carbon granular oral adsorbent C2 to ameliorate the doxorubicin-associated cardiohemodynamics changes and are the ground for further future investigation of different combinations of enterosorption and cardio-tropic drugs.

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Conflict of Interests

The authors declare no conflict of interest.

Author Contributions

Shevchuk O.O. – investigation, conceptualization, resources, writing – original draft; *Portnichenko G.V.* – formal analysis, visualization, investigation, writing – original draft, data curation, *Lapikova-Bryginska T.Y.* – investigation, data curation, *Goncharov S.V.* – investigation, data curation; *Nikolaev V.G.* – conceptualization, project administration, writing (review and editing), supervision; *Dosenko V.E.* – project administration, writing (review and editing), supervision.

ПОЗИТИВНИЙ ВПЛИВ ЕНТЕРОСОРБЦІЇ НА ПОРУШЕННЯ КАРДІОГЕМОДИНАМІКИ, СПРИЧИНЕНІ ДОКСОРУБІЦИНОМ

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1 – ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І.Я. ГОРБАЧЕВСЬКОГО,
ТЕРНОПІЛЬ, УКРАЇНА

2 – ІНСТИТУТ ФІЗІОЛОГІЇ ІМЕНІ О.О. БОГОМОЛЬЦЯ НАН УКРАЇНИ, КИЇВ, УКРАЇНА

3 – ІНСТИТУТ ЕКСПЕРИМЕНТАЛЬНОЇ ПАТОЛОГІЇ, ОНКОЛОГІЇ І РАДІОБІОЛОГІЇ ІМЕНІ Р.Є. КАВЕЦЬКОГО
НАН УКРАЇНИ, КИЇВ, УКРАЇНА

Вступ. Кардіотоксичність протипухлинних лікарських засобів, і особливо антрациклінових антибіотиків, є одним з лімітуючих факторів ефективного лікування злоякісних новоутворів.

Мета. Дослідити можливість ентеросорбції для пом'якшення кардіогемодинамічних змін, викликаних доксорубіцином в експерименті.

Методи. Субхронічна доксорубіцинова токсичність моделювалася чотирьохкратним введенням доксорубіцину інтраперитонеально в дозі 5 мг/кг один раз на тиждень протягом 4 тижнів у сумарній кумулятивній дозі 20 мг/кг. Щури були рандомізовані у 3 групи: контроль, група тварин, що отримувала доксорубіцин (DOX-група) та групу, котра окрім останнього отримувала ентеросорбент С2 ($\gamma=0.18$ г/см³, BET – 2162 м²/г). Параметри кардіогемодинаміки вивчалися за допомогою Millar Instruments, морфометричні зміни серця – за методом Автанділова.

Результати. Летальність у DOX-групі склала 25%. Показники фракції викиду та ударної роботи серця знижувалися порівняно з показниками контрольної групи. Показник максимальної потужності, зрівноваженої на переднавантаження був достовірно нижчим на 57,6%, а мінімальний об'єм та кінцево-систоличний об'єм зросли на 76,2 та 67,5%, що свідчить про розвиток застійних явищ. Показники $V@dPdt_{max}$ зросли на 73.3%, $V@dPdt_{min}$ – на 81.9%. Кінцево-діастолічний об'єм був вищим на 54.6%. Спостерігалася тенденція до зниження $dPdt_{min}$ та Тау константи. Ендокардіальна поверхня лівого шлуночка зросла на 42,7%, а планіметричний індекс – на 40,4%.

У групі DOX+C2 летальність склала 18,75%. Спостерігалася виражена тенденція до нормалізації усіх показників. Особливо ми хочемо підкреслити позитивний ефект застосування вуглецевого ентеросорбента С2 на показники фракції викиду (з $39.62 \pm 10.50\%$ до $46.23 \pm 11.46\%$) та ударної роботи (з 6406.50 ± 3345.83 до 10363.14 ± 7329.55 мм.рт.ст*мкл) як важливих показників насосної функції серця.

Висновки. В статті наведені дані, котрі демонструють здатність ентеральної сорбційної терапії зменшувати зрушення показників кардіогемодинаміки, спричинені введенням доксорубіцину. Окрім цього, ентеросорбція сприяла зменшенню показника летальності піддослідних тварин.

КЛЮЧОВІ СЛОВА: субхронічна доксорубіцинова токсичність; пошкодження серця; ентеросорбція; параметри кардіогемодинаміки.

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