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Metabolic myocardial protection in children with anthracycline cardiomyopathy

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Abstract
The article presents results of an investigation of the heart's systolic function and level of an atrial natriuretic peptide as a marker of heart failure in children with acute lymphoblastic leukemia and developed anthracycline cardiomyopathy as a result of chemotherapy protocol with doxorubicin. Distribution of children into groups conducted with regard to the use of cardioprotective metabolic therapy with medicinal product, in which the levocarnitine was an active substance. The first group of patients was cardioprotected and the second was not. Specified drug therapy began at the 39th day of the first phase of I protocol of the treatment of acute lymphoblastic leukemia and lasted till the end of I and mM protocols, and 2 weeks before the first phase II protocol. Assessment of systolic heart function was studied using echocardioscopy. Diagnosis of early signs of heart failure was made by determining the level of atrial natriuretic peptide. It was established that the cardioprotective therapy with medicinal product, in which the levocarnitine was an active substance, increases the contractile ability of the left ventricle, and also reduces the manifestations of systolic dysfunction and the level of heart failure marker.

Keywords: doxorubicin, cardiotoxicity, acute lymphoblastic leukemia, children.

1. Introduction
Progressiveness of oncohematological pathology among children and expansion of their treatment protocols using highly toxic chemotherapy drugs, need some new effective ways of pharmacological correction of complications developing.
Particularly noteworthy are anthracycline antibiotics (AA) (doxorubicin, daunorubicin, idarubicin, epirubicin, epidoxorubicin), which is known to be an integral part of hemoblastoses chemotherapy and other malignancies [1]. Clinical studies have shown that chemotherapy, which includes AA, helps to prevent the recurrence of the disease and thereby increase the survival of patients with oncohematological pathology [1]. However, it is known that AA can cause severe complications of the heart [2, 3, 4]. It is proved that usage of AA in children under 4 years leads to the death of a large number of cardiomyocytes (CMC), which further recovery is impossible even in adulthood [5, 6]. Of particular importance is the fact that anthracycline heart disease may not manifest clinically. However, despite this, the pathological process progresses and leads to the development of systolic dysfunction of left ventricular (LV) and to irreversible changes in the myocardium and consequently to congestive heart failure (CHF) [7].
It is know that death-rate with cardiac causes in patients which received AA is 0,6 – 7,0%, and with the development of CHF – 60,0 – 79,0% [8, 9]. Scientists suppose that the leading pathogenetic mechanism of anthracycline cardiomyopathy (ACCM) is the damage of myocardium mitochondria infarction. It was noted the tropism of AA to mitochondrial cardiolipin-phospholipid membranes of heart muscle [9, 10]. Also, it was proved that AA violate the carnitine-dependent metabolism in the myocardium lipid by reducing the polyunsaturated fat acids CMC [10]. As a result of the energy inhibition of myocardium, the primary hypoxic disorders are developed. It leads to accumulation of large quantities of oxidized fat acids in the mitochondria and have an ability to destroy the cell membrane [11, 12].
Drawing attention to the growing spread of acute leukemia in children, the widely usage of protocol anthracycline therapy and the growth of anthracycline cardiomyopathy, it is needed to conduct a medical correction in time. It can help to prevent the complications and reduce the possibility of further disease progression.

The research purpose is to determine the advisability and possibility of metabolic therapy with medicinal product, in which the levocarnitine is an active substance, in children with anthracycline cardiomyopathy in the background of acute lymphoblastic leukemia.

2. Materials and methods

Inspection and retrospective analysis were done for 70 case histories of children aged from 3 to 15 with acute lymphoblastic leukemia (ALL) and developed secondary toxic ACCM as a result of protocol PCT, which were hospitalized in Ivano-Frankivsk Regional Pediatric Hospital in 2008 – 2015. Patients were randomized into two groups. The first group – 35 children treated with cardioprotective therapy; the second – 35 children without the treatment. From the 39th day of the first chemotherapy protocol the Ahvantar (20% levocarnitine solution for oral usage) was used for cardioprotection (LLC "Ersel Pharma Ukraine", №UA/11554/01/01, 06.09.2011 – 09.06.2016). The initial dose was 50 mg/kg/day, but in 2 weeks it was doubled up to 100 mg/kg/day taken in three doses, 30 minutes before food intake. Duration – 60 – 90 days (the end of the first and the second phase of I protocol, 2 weeks after I protocol, mM protocol, 2 weeks before II protocol).

Depending on the cumulative dose of AA (doxorubicin) (DR), the patients of both groups were divided into three subgroups: I A (n = 11) and II A (n = 10) groups – children aged from 3 to 6 with the cumulative dose of DR 100,0 – 200,0 mg/m^2; I B (n = 11) and II B (n = 12) groups – aged from 7 to 10 with the cumulative dose of DR 200,0 – 300,0 mg/m^2; I C (n = 13) and II C (n = 13) groups – aged from 11 to 15 with the cumulative dose of DR 300,0 – 400,0 mg/m^2. The control group was 20 practically health children of similar age with patients.

The EhoCS-study and the determination of atrial natriuretic peptide level (NT-pro-BNP) were conducted during clinical and laboratory tests for all inspected patients on 14th and 30th day after beginning of PCT with the inclusion of doxorubicin.

LV systolic function was assessed by the following indicators: the end-diastolic and the end-systolic volumes (EDV, ESV), the stroke volume (SV), the minute volume of blood (MVB), the left ventricular ejection fraction (LVEF), the interventricular septum thickness (T_{IVS}, cm) and the LV posterior wall (T_{LVPW}, cm), the pressure in the pulmonary artery (PA). The end diastolic (EDI) and the systolic (ESI) indexes were calculated by the following formulas (1, 2):

$$EDI = EDV / BE \quad (1)$$

$$ESI = ESV / BE \quad (2)$$

where BE – body surface area (m^2) [11, 12].

The mass of left ventricular (MLV) is determined by the Troy formula (3) [13]:

$$MLV = 0{,}8 \cdot \{1{,}04 \cdot ([EDS+T_M+T_{IVS}]^3-[EDS]^3)\}+0.6 \quad (3)$$

The myocardial mass index (MMI) was calculated as the ratio of MLV to BE (cm/m^2) by the formula (4) [11, 12]:

$$MMI = MLV / BE\ (g/m^2) \quad (4)$$

The study was conducted on the PHILIPS machine «En Visor C HD» using echocardiography (in B- and M- modes) and doplerechocardiography with a sensor frequency 3.5 MHz.

Quantitative assessment of concentrations of NT-pro-BNP (pg/ml) in children's blood plasma was performed by the electrochemiluminescent immunoassay ECLA method using polyclonal antibodies on automatic analyzers of "Hoffmann-La Roche": Yeleksys 1010, 2010, and E170 Modular test system "Yeleksys proBNP" company "Roche" (Switzerland).

The criterion for the appointment of the drug with the levocarnitine active ingredient, was identification of EhoCS-change (decrease of left ventricular contractile capacity, growth of MLV and EDI (ESI), heterogeneity of myocardium echo structure) and increase of NT-pro-BNP more than 80 pg/ml. EhoCS check was performed once per 10 days (or when deterioration), and re-determination of NT-pro-BNP – in 45 – 60 days. With the normalization of all parameters, a course of the levocarnitine therapy was 60 days, but in case of maintaining functional and laboratory abnormalities – prolonged to 90 days.

Statistical data processing was performed using Statistica software of package 5.5A (StatSoft, USA). The average values presented in the form of M ± m, where M – the average rate, m – standard error of the mean. The Student criterion was used during comparing the average values. Results considered statistically significant for values of $p<0{,}05$.

3. Results and their discussion

The growth of T_{LVPW} and T_{IVS} with each following chemotherapy protocol was detected during observation of children with ACCM on background of ALL. The average values of these parameters were highest at the end of the first phase of II protocol (0,84±0,01 cm), which is significantly different from those during the first visit of patients ($p<0{,}001$) and healthy children ($p_N<0{,}001$) (Table 1).

Table 1: EhoCS features – PCT length parameters (M±m) of the healthy children and of the II group children with ACCM.

(M±m)

Indexes	Healthy[1] (n=20)	Children with ACCM II group			
		I visit[2] (n=35)	1 phase I P[3] (n=35)	mM-P[4] (n=34)	1 phase II P[5] (n=34)
1	2	3	1	2	3
Preasure PA, mm. Hg.	14,90±0,2	16,34±0,16 $P_{1-2}<0{,}01$	17,29±0,15 $P_{1-3}<0{,}001$ $P_{2-3}<0{,}001$	16,74±0,17 $P_{1-4}<0{,}01$	17,47±0,14 $P_{1-5}<0{,}001$ $P_{2-5}<0{,}001$ $P_{4-5}<0{,}001$
T_{IVS},cm	0,53±0,01	0,65±0,01 $P_{1-2}<0{,}001$	0,73±0,01 $P_{1-3}<0{,}001$ $P_{2-3}<0{,}001$	0,73±0,01 $P_{1-4}<0{,}001$ $P_{2-4}<0{,}001$	0,84±0,01 $P_{1-5}<0{,}001$ $P_{2-5}<0{,}001$ $P_{3-5}<0{,}001$ $P_{4-5}<0{,}001$
T_{LVPW}, cm	0,53±0,01	0,65±0,01 $P_{1-2}<0{,}001$	0,73±0,01 $P_{1-3}<0{,}001$ $P_{2-3}<0{,}001$	0,73±0,01 $P_{1-4}<0{,}001$ $P_{2-3}<0{,}01$ $P_{3-4}<0{,}001$	0,84±0,01 $P_{1-5}<0{,}001$ $P_{2-5}<0{,}001$ $P_{3-5}<0{,}001$ $P_{4-5}<0{,}001$
ESI, ml/m^2	17,75±0,37	20,34±0,49	25,30±0,46 $P_{1-3}<0{,}05$ $P_{2-3}<0{,}001$	24,74±0,42 $P_{2-3}<0{,}01$ $P_{3-4}<0{,}001$	29,23±0,53 $P_{1-5}<0{,}001$ $P_{2-5}<0{,}001$ $P_{3-5}<0{,}001$ $P_{4-5}<0{,}001$
EDI, ml/m^2	56,33±1,21	58,30±0,94	64,63±1,05 $P_{1-3}<0{,}001$	64,77±0,98 $P_{1-4}<0{,}05$	72,22±1,18 $P_{1-5}<0{,}001$

			P_{2-3}<0,001	P_{2-3}<0,05 P_{3-4}<0,05	P_{2-5}<0,001 P_{3-5}<0,001 P_{4-5}<0,001
HSV, ml	36,87±0,83	41,23±1,02	42,35±0,97 P_{2-3}<0,05	42,64±0,98	45,97±0,98 P_{1-5}<0,001 P_{2-5}<0,01 P_{3-5}<0,05 P_{4-5}<0,001
HMV, l/min	3090,4±64,8	4150,5±90,6	5126,6±122,8 P_{1-3}<0,001 P_{2-3}<0,001	4476,5±108,4 P_{1-4}<0,001 P_{2-3}<0,01 P_{3-4}<0,05	5445,9±120,7 P_{1-5}<0,001 P_{2-5}<0,001 P_{3-5}<0,05 P_{4-5}<0,001
EF, %	68,45±0,13	65,37±0,38 P_{1-2}<0,001	60,60±0,27 P_{1-3}<0,001 P_{2-3}<0,001	62,06±0,22 P_{1-4}<0,001 P_{3-4}<0,05	59,15±0,23 P_{1-5}<0,001 P_{2-5}<0,001 P_{4-5}<0,001
LVMM, g	46,81±2,06	69,22±2,44 P_{1-2}<0,01	85,03±2,74 P_{1-3}<0,001 P_{2-3}<0,001	84,65±2,54 P_{1-4}<0,001 P_{2-3}<0,01	109,57±3,27 P_{1-5}<0,001 P_{2-5}<0,001 P_{3-5}<0,001 P_{4-5}<0,001
LVMMI, g/m^2	46,97±1,35	61,69±1,32 P_{1-2}<0,001	75,95±1,77 P_{1-3}<0,001 P_{2-3}<0,001	77,95±1,51 P_{1-4}<0,001 P_{2-3}<0,001 P_{3-4}<0,001	100,94±2,50 P_{1-5}<0,001 P_{2-5}<0,001 P_{3-5}<0,001 P_{4-5}<0,001

Note: P - probable difference of EchoKS parameters in healthy children (1) and in children with ACCM during the first visit (2), after the first phase of I P (3), after mM-P (4), and after the first phase of II protocol (5)

Similar situation was observed in patients of I group for the period of I and mM protocols. However, at the end of the first phase of II protocol, and after the levocarnitine protocol metabolic therapies, the average values of the parameters did not differ significantly from those at the first visit (Table 2).

Table 2: EhoCS features – parameters of healthy children and of II group children with ACCM which received levocarnitine.

(M±m)

Indexes	Healthy[1] (n=20)	Children with ACCM II group			
		I visit[2] (n=35)	1 phase I P[3] (n=35)	mM-P[4] (n=34)	1 phase II P[5] (n=34)
1	2	3	4	5	6
Preasure PA, mm. Hg.	14,90±0,2	16,66±0,17 P_{1-2}<0,01	17,46±0,18 P_{1-3}<0,001 P_{2-3}<0,01	16,06±0,16 P_{1-4}<0,05 P_{3-4}<0,05	15,17±0,15 P_{3-5}<0,01
T_{IVS},cm	0,53±0,01	0,68±0,01 P_{1-2}<0,001	0,83±0,01 P_{1-3}<0,001 P_{2-3}<0,01	0,73±0,01 P_{1-4}<0,001 P_{2-4}<0,05	0,64±0,01 P_{1-5}<0,01 P_{3-5}<0,01 P_{4-5}<0,001
T_{LVPW}, cm	0,53±0,01	0,69±0,01 P_{1-2}<0,001	0,81±0,02 P_{1-3}<0,001 P_{2-3}<0,01	0,73±0,01 P_{1-4}<0,001 P_{3-4}<0,05	0,64±0,01 P_{1-5}<0,01 P_{3-5}<0,001 P_{4-5}<0,001
ESI, ml/m^2	17,75±0,37	22,87±0,54 P_{1-2}<0,01	29,02±0,44 P_{1-3}<0,001 P_{2-3}<0,001	22,73±0,30 P_{1-4}<0,001 P_{3-4}<0,001	20,02±0,38 P_{3-5}<0,001
EDI, ml/m^2	56,33±1,21	62,08±1,06	72,65±1,04 P_{1-3}<0,001 P_{2-3}<0,001	64,40±0,88 P_{1-4}<0,01 P_{3-4}<0,01	56,34±0,92 P_{3-5}<0,01
HSV, ml	36,87±0,83	43,63±1,18	45,30±1,16 P_{1-3}<0,05 P_{2-3}<0,05	45,01±1,22 P_{1-4}<0,05	42,04±1,22 P_{3-5}<0,01
HMV, l/min	3090,4±64,8	3930,4±86,4 P_{1-2}<0,01	5678,9±127,4 P_{1-3}<0,001 P_{2-3}<0,001	3900,3±74,9 P_{1-4}<0,001 P_{3-4}<0,01	3889,9±104,1 P_{1-5}<0,01 P_{3-5}<0,01
EF, %	68,45±0,13	65,43±0,18 P_{1-2}<0,001	59,66±0,2 P_{1-3}<0,001 P_{2-3}<0,001	64,60±0,18 P_{1-4}<0,001 P_{3-4}<0,001	66,23±0,14 P_{1-5}<0,001 P_{3-5}<0,001
LVMM, g	46,81±2,06	78,09±3,16 P_{1-2}<0,01	107,99±4,33 P_{1-3}<0,001	87,60±3,11 P_{1-4}<0,001	68,11±2,79 P_{1-5}<0,05 P_{2-5}<0,05 P_{3-5}<0,05 P_{4-5}<0,05
LVMMI, g/m^2	46,97±1,35	70,65±1,56 P_{1-2}<0,001	100,47±2,19 P_{1-3}<0,001 P_{2-3}<0,05	78,44±1,63 P_{1-4}<0,001	58,67±1,06 P_{1-5}<0,01 P_{2-5}<0,05 P_{3-5}<0,05 P_{4-5}<0,05

Note: P - probable difference of EchoKS parameters in healthy children (1) and in children with ACCM during the first visit (2), after the first phase of I P (3), after mM-P (4), and after the first phase of II protocol (5)

Comparison of T_{IVS} and T_{LVPW} in I and II groups showed significant data difference only at the end of I phase of II protocol ($p<0,001$) (Table 3).

ESI index in children of II group tended to gradually increasing with the dominance of the parameters and at the end of the I (25,30±0,46) (ml/m^2) and the II (29,23±0,53) (ml/m^2) protocols; was likely compared with that in healthy children (p_N <0,001) (see Table 1). Analysis of the ESI index in patients of I group was similar to the data in the II group, before receiving of medicinal product, in which the levocarnitine was an active substance. However, after taking of metabolic therapy the average ESI was decreased (20,02 ±0,38) (ml/m^2) and was not statistically different from the average ESI at the first visit to these patients, but also from the average ESI of comparison group (see Table 2).

It was detected an increasing of average EDI as a result of the AA use. It should be noted that the highest rate of EDI in children of II group was at the end of I phase of II protocol (72,22±1,18) (ml/m^2) and was significantly different from the first visit rate ($p<0,001$) and from the control group rate ($p_N<0,001$) (see Table 1). The highest rate of EDI in children of I group was at the end of I phase of I protocol (72,65±1,04) (ml/m^2) and was significantly different from the first visit rate ($p<0,001$) and from the control group rate ($p_N<0,001$) (see Table 2). After mM-protocol, the EDI in patients of I group was different from the first visit rate, also a significant difference was detected during comparison with the control group rate ($p_N<0,01$).

The growth of HSV in patients of II group has occurred since the end of the first phase of I protocol and tended to gradual increasing with each subsequent chemotherapy protocol. The maximum of HSV in this group of patients was at the end of the I phase of II protocol (45,97±0,98) (ml) and was significantly different from that at the first visit ($p<0,001$) and in the control group ($p_N<0,001$) (see Table 1). It should be noted that averages of HSV in patients of I group had no significant fluctuations, and at the end of the I phase of II Protocol, on the background of cardioprotective therapy, the rate was (42,04±1,22) (ml) and significantly differed from this at the end of the I phase of I protocol ($p<0,01$) (see Table 2).

A similar trend was observed for HMV rate (l/min). On a background of all CTs, the indicator in patients was significantly higher than in healthy children. The HMV growth was recorded in observed children of II group already at the first visit (4150,46±90,57) (l/min), but the maximum HMV average values were detected at the end of I phase of I- (5126,60±122,81) (l/min) and of II- (5445,89±120,70) (l/min) protocols, and were significantly different from the HMV values in the comparison group ($p_N<0,001$) (see Table 1). In patients of I group the HMV growth was recorded only at the end of the I phase of I protocol (5678,94±127,39) (l/min) ($p_N<0,001$), but in the end Mm- (3900,32±74,94) (l/min) and II- (3889,98±104,05) (l/min) protocols the averages were different from those at the first visit (see Table 2). It should be noted that in the period of examination, on the background of cardioprotection, between the indicators of HMV in patients of I and II groups the significant difference was observed: ($p<0,05$) and ($p<0,001$) respectively (see Table 3).

During analysis of EF rates (%) in the II group of children with ACCM, it was observed a probable decrease of contractile ability of LV ($p_N<0,001$). Minimum of EF was in patients of the II group at the end of the I phase of I- (56,60±0,27) (%) and II- (57,15 ± 0,23) (%) protocols ($p_N<0,001$) (see Table 1). The similar situation was observed in the I group of patients and at the end of the I phase of I protocol, where the EF was minimal (57,66±0,2) (%), and significantly differed from the EF at the first visit and in the control group ($p<0,001$) (see Table 2). It should be noted that normalization of the myocardial contractile function in patients treated with medicinal product, in which the levocarnitine was an active substance, was observed at the end of Mm and II protocols, and their EF was (64,60±0,18) (%) and (66,23±0,14) (%), respectively. It was established a significant difference during comparison of EF rates in patients of I and II groups at the end of Mm and II protocols ($p<0,001$) (see Table 3).

It should be noted that in patients of II group, which have not received metabolic therapy, it was detected an increase of LVMM (g) at all stages of the survey ($p_N<0,001$), but the maximum was at the end of the I phase of II protocol (109,57±3,27) (g), and was significantly differed from the comparison group ($p_N<0,001$) (see Table 1). In children of I group the LVMM was the highest at the end of the I phase of I protocol (107,99±4,33) (g), and significantly differed from the control group ($p_N<0,001$). However, on the background of cardioprotective therapy, at the end of the I phase of II protocol, the average LVMM of the patients of I group had decreased (68,11±2,79) (g), but at the same time was significantly different from the first visit averages and the rates of control group ($p<0,05$) (see Table 2). The LVMM comparison of the patients who were on the levocarnitine therapy and the patients who did not receive the metabolic therapy, showed reliability of the difference ($p<0,001$) at the end of I phase of II protocol (see Table 3).

Table 3: The comparison of EhoKS parameters in children with ACCM in the background of the levocarnitine therapy and in children with ACCM without the levocarnitine therapy

(M±m)

Indexes	Children with ACCM[1] I group				Children with ACCM[2] II group			
	I visit n=35	1 phase I P n=35	mM-P n=35	1 phase II P n=35	I visit n=35	1 phase I P n=35	mM-P n=34	1 phase II P n=34
1	2	3	4	5	6	7	8	9
Preasure PA, mm.Hg.	16,66±0,17	17,46±0,18	16,06±0,16	15,17±0,15	16,34±0,16	17,29±0,15	16,74±0,17	17,47±0,14 $P_{1-2}<0,001$
T_{IVS},cm	0,68±0,01	0,83±0,01	0,73±0,01	0,64±0,01	0,65±0,01	0,73±0,01 $P_{1-2}<0,01$	0,73±0,01	0,84±0,01 $P_{1-2}<0,001$
T_{LVPW}, cm	0,69±0,01	0,81±0,02	0,73±0,01	0,64±0,01	0,65±0,01	0,73±0,01	0,73±0,01	0,84±0,01 $P_{1-2}<0,001$
ESI, ml/m^2	22,87±0,54	29,02±0,44	22,73±0,30	20,02±0,38	20,34±0,49	25,30±0,46 $P_{1-2}<0,01$	24,74±0,42	29,23±0,53 $P_{1-2}<0,001$
EDI, ml/m^2	62,08±1,06	72,65±1,04	64,40±0,88	56,34±0,92	58,30±0,94	64,63±1,05 $P_{1-2}<0,01$	64,77±0,98	72,22±1,18 $P_{1-2}<0,001$
HSV, ml	43,63±1,18	45,30±1,16	45,01±1,22	42,04±1,22	41,23±1,02	42,35±0,97	42,64±0,98	45,97±0,98

HMV, l/min	3930,4±86,4	5678,9±127,4	3900,3±74,9	3889,9±104,1	4150,5±90,6	5126,6±122,8	4476,5±108,4 P_{1-2}<0,05	5445,9±120,7 P_{1-2}<0,001
EF, %	65,43±0,18	59,66±0,2	64,60±0,18	66,23±0,14	65,37±0,38	60,60±0,27	62,06±0,22 P_{1-2}<0,001	59,15±0,23 P_{1-2}<0,001
LVMM, g	78,09±3,16	107,99±4,33	87,60±3,11	68,11±2,79	69,22±2,44	85,03±2,74 P_{1-2}<0,05	84,65±2,54	109,57±3,27 P_{1-2}<0,001
LVMMI, g/m^2	70,65±1,56	100,47±2,19	78,44±1,63	58,67±1,06	61,69±1,32 P_{1-2}<0,05	75,95±1,77 P_{1-2}<0,001	77,95±1,51	100,94±2,50 P_{1-2}<0,001

The similar situation was observed during analysis of LVMM averages in patients with ACCM. The LVMM maximum rates in patients of II group were recorded at the end of the I phase of II protocol (100,94±2,50) (g/m2), and were significantly different from the first visit rates (before PCT) ($p<0,001$) and those in control group (see Table 1).

A weighty growth of LVMMI rate in patients of I group at the end of the I first phase of I protocol (100,47±2,19) (g / m2), after metabolic therapy, was changed with a decrease of this index in almost twice (58,67 ±1,06) (g/m2), but at the same time still was significantly differed from the control group ($p_N<0,001$) (see Table 2).

The study of atrial natriuretic peptide (NT-pro-BNP) in children on AA chemotherapy protocol showed growth at the end of the I phase of I protocol in patients of both groups to (208,35±9,99) (pg/ml) and to (196,76±8,83) (pg/ml) respectively ($p_N<0,001$). Against the background of cardioprotective therapies, a possible decline of NT-pro-BNP to (61,99±1,07) (pg/ml) was observed in patients of I group ($p<0,001$), however, the difference of those in the control group remained significant ($p_N<0,05$) (Table 4).

Table 4: The level of atrial natriuretic peptide in healthy children and in children with anthracycline cardiomyopathy.

(M±m)

Index	Healthy[1] (n=20)	
NT-pro-BNP, pg/mL	46,85±3,32	
	Children with ACCM	
	I group[2] n=35	II group[3] n=35
1 phase of I P[3]		
NT-pro-BNP, pg/mL	208,35±9,99 P_{1-2}<0,001	196,76±8,83 P_{1-3}<0,001
1 Phase of II P[4]		
NT-pro-BNP, pg/mL	61,99±1,07 P_{1-2}<0,05 P_{3-4}<0,001	-

Note: P – probable difference of the parameter in healthy (1) children, in children with ACCM of I (2) and II (3) groups, in children of I group in I phase of I P (3) and of I phase of II P (4).

This indicates that metabolic therapy with medicinal product with the levocarnitine active substance, gradually reduces the marker of asymptomatic heart failure in children with ACCM on the background of ALL, and has positive therapeutic effect on elimination of toxic myocardial injury from anthracycline antibiotics.

4. Conclusions

The therapy by medicinal product with the levocarnitine active substance of patients with anthracycline cardiomyopathy in background of acute lymphoblastic leukemia prevents the development of left ventricular hypertrophy, reduces the signs of the left ventricular systolic dysfunction and simultaneously increases its contractile capacity, reduces the chances of developing of the heart failure in this category of patients.

5. Prospects for further research

It is planned to identify the early markers of myocardial damage in children with ACCM and examine the effectiveness of cardioprotective therapy with medicinal product with the levocarnitine active substance for correction or prevention of myocardial damage.

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