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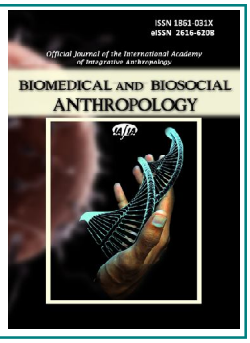

Study of morphological changes in the kidney during modeling of ischemic-reperfusion injuries of the limb and massive blood loss

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The article presents the features of morphological disorders of liver tissue on the background of limb ischemia-reperfusion and massive blood loss. The aim of the work was to establish the presence of structural changes and the severity of morphological disorders of internal organs, remote from the primary place of ischemia-reperfusion during modeling the pathological process. The experiment was performed on 33 adult nonlinear white rats weighing 200-250 g, which were on the standard vivarium diet. Experimental animals were simulated with ischemic-reperfusion syndrome of the lower extremity and massive blood loss. Collection of materials was performed 1 h after intervention or release from the tourniquet and on the 1st, 3rd, 7th and 14th days. All interventions were performed under thiopental-sodium anesthesia (40 mg/kg body weight). Mostly structural violations were expressed as disturbance of blood supply of little and middle caliber blood vessels and also in initial dystrophic changes. During comparison of groups, depending on the severity, it was shown that both the isolated use of a tourniquet and massive blood loss had long-term, systemic consequences, however, more expressed in EG-2; single vascular glomeruli were shrunked, endothelial cells of arterioles were slightly damaged. On the 7th and 14th days changes in the structure of EG-1 were mostly absent, although in EG-2 the epitheliocytes of the outer layer of the capsule remained flattened, retained full blood vessels of the venous bed in the interstitium, and the vast majority of epitheliocytes of the excretory tubules were at different stages of hydropic dystrophy with partly desquamation of the epithelium in the gaps of the tubules. Also, the basal membranes of the tubules were not completely visualized, which indicates deep damage in the structures caused by acute ischemia as a result of bleeding. Thus, as combat trauma (blood loss) is in itself a life-threatening factor, the use of a tourniquet due to the development of ischemic-reperfusion process can complicate the course of the primary affection. Knowledge of the periodization of traumatic disease on the background of this pathology is important for the development of sanogenic effects in order to minimize this pathogenic factor.

Key words: *hemostatic tourniquet, kidney, experiment, ischemic-reperfusion syndrome, blood loss).*

Introduction

The use of a tourniquet is still an important first aid measure [11, 13]. Active battles that occur periodically in the modern world, including in Ukraine, are accompanied with injuries and blood loss and require careful study of the mechanisms of posttraumatic period. A significant role of ischemic-reperfusion syndrome due to the use of tourniquet now is actively discussed [1, 9]. There are materials in the literature that highlight the ambiguity of reperfusion changes as a result use of a tourniquet.

The pathogenesis of the process is based not only on hemic hypoxia, but also on the combination of its consequences with manifestations of rhabdomyolysis and massive entry into the systemic bloodstream of products of lipid and protein peroxidation from exsanguinated tissues [4]. The morphological changes of skeletal muscles that were under pressure of the tourniquet were best studied [18]; they consisted of dystrophic changes in muscle fibers and were apparently caused by a violation of ionic composition, an imbalance of metabolic processes due to a shift in acid-base balance on the background of tissue hypoxia. In particular, the structural changes of the soft tissues of the extremities and modifications in the

microcirculatory tract [10, 15, 22] on the background of this syndrome were studied.

There are morphologically confirmed data about lungs changes on the background of modeling ischemic and reperfusion injuries of the limb [19]; however, in this case the ischemia lasted 4 hours and led to a significant disturbance in the microcirculatory tract without signs of an inflammatory reaction. In the reperfusion stage morphological changes were found. It corresponded to the expression of the second phase of respiratory distress syndrome; changes in the structure of the large joints of the lower extremities were also recorded in conditions of combined abdominal and skeletal trauma in combination with ischemia-reperfusion [14].

The consequences of massive blood loss in accordance to the statistics, study of the ambiguous effects of limb ischemia-reperfusion with the next use of tourniquet has particular importance - as the release of biologically active substances from endothelial cells, cytokine storm, which may have systemic effects. However, these aspects are still not enough studied.

The aim of the work was to establish the presence of structural changes and the severity of morphological disorders of the tissues of internal organ, remote from the primary place of ischemia-reperfusion during modeling the pathological process.

Materials and methods

The experimental study was performed on 33 adult nonlinear white male rats weighing 200-250 g, which were on the standard mode of keeping the vivarium. Animals were divided into 3 groups: EG-1 - the use of a tourniquet on the thigh for 2 h (isolated ischemia-reperfusion); EG-2 - simulation of blood loss and control group.

The interventions were performed under conditions of thiopental-sodium anesthesia (40 mg/kg) in consideration with the rules of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (European Convention, 1984) and Law of the Ministry of Health of Ukraine № 690, considered by the commission at a meeting of the commission on bioethics of I. Ya. Gorbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine № 61 by 11.01.2020.

In EG1 animal were simulated with ischemia-reperfusion of the limb. Under thiopental-sodium anesthesia (40 mg/kg body weight intraperitoneal), SWAT-T (US) tourniquet with width 10 mm was applied to the thigh of an animal and adequately corresponds pressure of the tourniquet when applied to the thigh of an adult human. According to the literature, such a tourniquet is characterized by minimal negative traumatic effects on the underlying tissues due to its width and long-term pain threshold. The tourniquet was tightened according to the applied effective pressure marking, which is able to stop the blood flow. In EG2 under conditions of anesthesia, acute heavy blood loss (up to 40 % of volume of circulating blood) was modeled by puncture of the femoral vein with farther hemostasis.

The morphological study of tissue sections of the kidney was performed and documented according to the generally accepted method with hematoxylin-eosin staining using a LOMO Biolam I microscope.

Results

Histological examination of the animals' kidneys (in EG-1) on the 1st day after the intervention on the background of isolated use of a tourniquet revealed uneven blood supply to the organ with mostly reduced blood supply to the cortical layer and partial hyperemia of the medullar layer (Fig. 1).

The size of the glomeruli decreased, their lumens narrowed due to decreased blood supply or spasms. The structure of the glomeruli remained mostly preserved, the nephrothelium of the inner layer of the capsule shrunken slightly. The stroma of the organ was weakly visualized. Manifestations of edema in the interstitium were not observed. In the vast majority of excretory tubules, the renal lumen did not dilate and was not clearly visualized. Manifestations of changes in epitheliocytes were not expressed.

Histological examination of the animals' kidneys on the 7th day of the experiment revealed, as in the previous stage, uneven blood supply to the organ with mostly reduced blood supply of the cortical layer and partial hyperemia of the medullar layer (Fig. 2).

The size of the glomeruli remained reduced due to the reduced blood supply in the vessels, the structure of the glomeruli remained mostly preserved, and the lumens of single vessels partially expanded. The lumens of some glomeruli expanded moderately, the nephrothelium

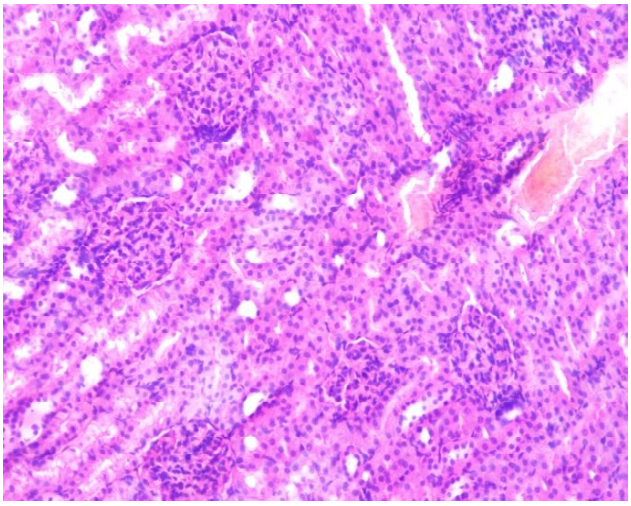

Fig. 1. The structure of the kidney on the 1st day after modeling of ischemia. Spasms of the vessels of the glomerular layer, decreased blood supply in the vessels of the cortical layer, narrowing of the lumen of the capsule. Staining with hematoxylin and eosin. x200.

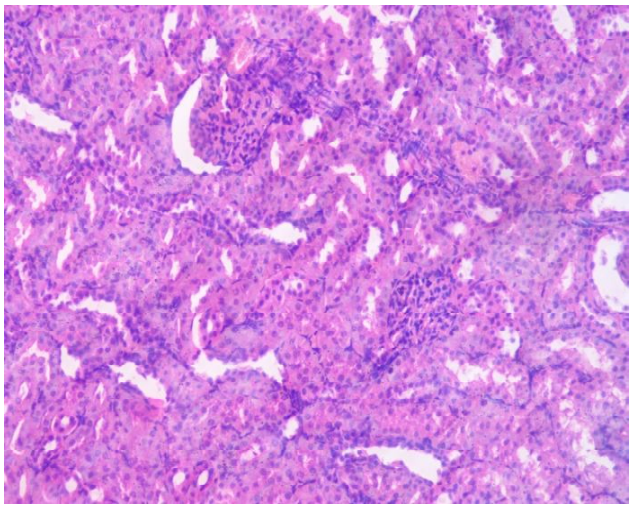

Fig. 2. The structure of the kidney on the 7th day after modeling ischemia. Reduced blood supply in the vessels of the glomeruli. Hematoxylin and eosin staining. x200.

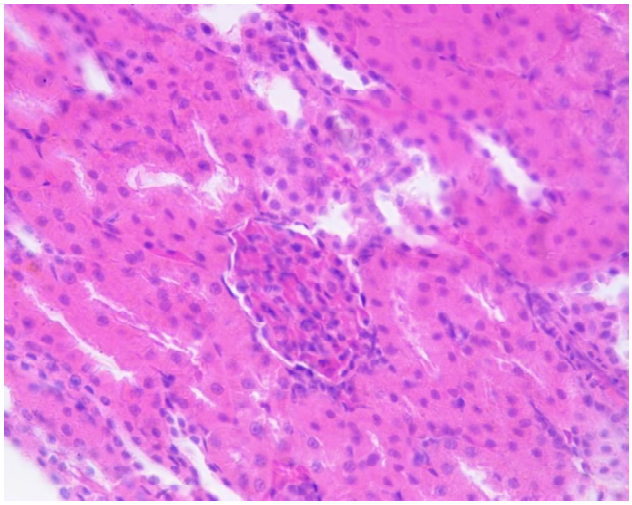

Fig. 3. The structure of the kidney on the 14th day after the simulation of ischemia. Equable blood supply of glomerular vessels, epithelium of excretory tubules without visible changes. Staining with hematoxylin and eosin. x200.

remained flattened. The stroma of the organ was poorly visible. Manifestations of edema in the interstitium were not observed. The vessels of the predominantly venous layer were visualized to be moderately dilated and full-blooded, but perivascular edema was absent. In several of the excretory tubules the lumens expanded moderately, some contained fibrinous layers. Manifestations of changes in epitheliocytes remained minimal.

Histological examination of the animals' kidneys of animals on the 14th day of the experiment revealed the restoration of blood supply in the vessels of both the cortical and medullar layers. The size of the glomeruli was increased, and vessels with moderate blood supply were well visualized. The lumens of the glomeruli had a normal structure, the structure of the nephrothelium was restored. Manifestations of edema in the interstitium were not observed. In the interstitium of the medullar layer, the vessels had a equable blood supply, perivascular edema was not observed. The lumens of the excretory tubules remained normal. Manifestations of changes in epitheliocytes remained minimal (Fig. 3).

Histological examination of the kidney in EG-2, on the background of modeling of isolated massive blood loss on the 3rd day after the intervention revealed reduced blood supply in the cortical and cerebral matter. The structure of the glomeruli remained predominantly preserved, the blood supply of the vessels of several glomeruli decreased, single vascular glomeruli were shrunken and endothelial cells of arterioles were slightly damaged. The lumens of the capsule slightly expanded. The epitheliocytes of the outer layers of the capsule shrunken, but were visualized in almost all glomeruli.

In the interstitium, the lumens of the vessels of the venous bed slightly expanded. The structure of a small number of epitheliocytes of the excretory tubules had different stages of development of protein dystrophy, in a some of them signs of apoptosis were present. Nuclei were visualized in the vast majority of cells, some of which were hyperchromic, with the presence of nucleoli, located basally, intercellular contacts remained mostly preserved. The lumens of the vast majority of excretory tubules were slightly dilated, containing minimal inclusions (Fig. 4).

Examination of the kidneys on the 7th day after the experiment revealed a moderate increase in blood supply of the cortical and medullar matter. The structure of the glomeruli remained mostly preserved, the blood supply of the vessels of some glomeruli increased significantly, the size of the vascular glomeruli increased. Some endothelial cells were lost. The lumens of the capsule were practically not visualized. The epitheliocytes of the outer layer of the capsule were moderately flattened.

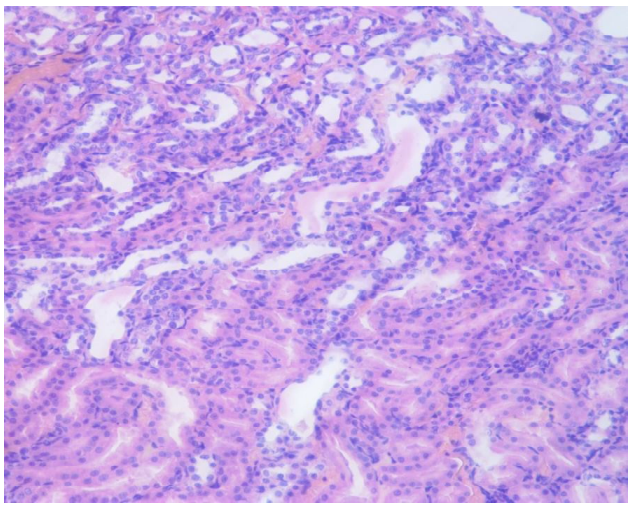

Fig. 4. The structure of the kidney on the 3rd day after the simulation of bleeding. Reduced blood supply in blood vessels, areas of expansion of the excretory tubules. Staining with hematoxylin and eosin. x200.

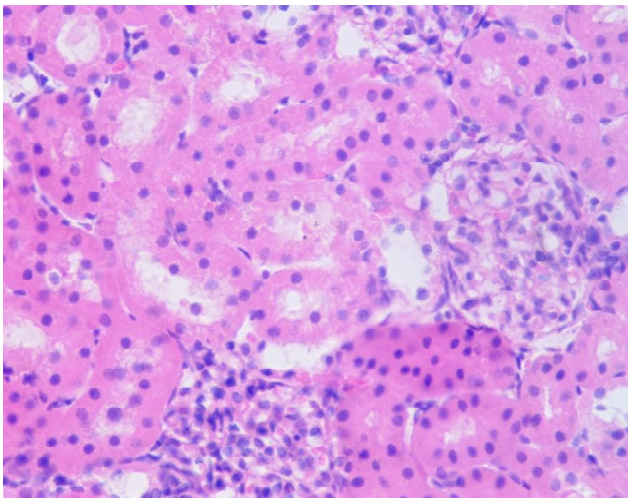

Fig. 5. The structure of the kidney on the 7th day after the simulation of bleeding. Dystrophic-necrotic changes of epitheliocytes of excretory tubules, partial damage of basal membranes. Hematoxylin and eosin staining. x400.

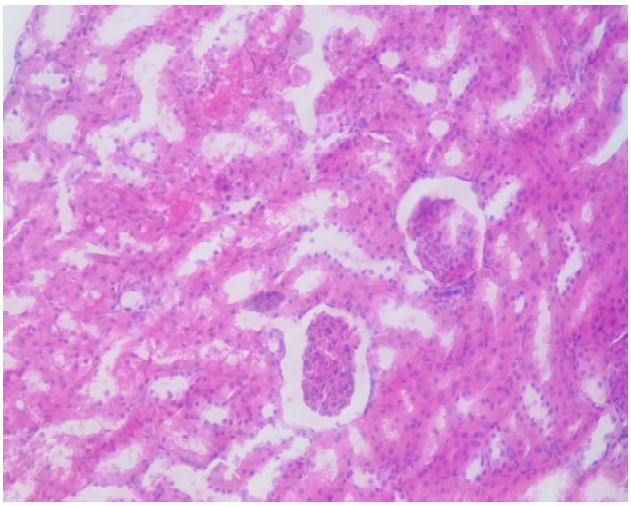

Fig. 6. The structure of the kidney on the 14th day after the simulation of bleeding. Hydropic dystrophy of epitheliocytes of excretory tubules, damage of basal membranes, wrinkling of vascular glomeruli. Staining with hematoxylin and eosin. x200.

In the interstitium, the lumens of the vessels of the venous bed were moderately dilated, somewhere full-blooded. The structure of the vast majority of epitheliocytes of the excretory tubules had different stages of development of protein dystrophy, some of them were with signs of apoptosis. Nuclei were visualized in the vast majority of cells, but their location was different. The cytoplasm of a large part of the cells became granular or enlightened, the cell nuclei were lost, which indicates the development of dystrophic-necrotic changes. The basal membranes of the tubules were partially damaged (Fig. 5). The lumens of the vast majority of excretory tubules were slightly dilated, containing fragments of cellular structures.

Examination of the kidneys on the 14th day after the experiment revealed a moderate increase in blood supply in the cortical and medullar matter. The glomeruli shrunken, the blood supply of the vessels of single glomeruli decreased, the size of the vascular glomeruli was not changed. Some endothelial cells remained lost. The lumens of the capsule were expanded. The epitheliocytes of the outer layer of the capsule remained flattened.

In the interstitium, the lumens of the vessels of the venous bed remained full-blooded. The vast majority of epitheliocytes of the excretory tubules were at different stages of development of hydropic dystrophy with focal desquamation of the epithelium in the tubules gaps. The basal membranes of the tubules were not partially visualized, which indicates deep damage to the structures caused by acute ischemia due to bleeding. Nuclei were visualized in the vast majority of cells, but their location, as in the previous group of studies, was different. The cytoplasm of a large part of the cells was homogeneous, homogeneous, a significant part of the basement membranes remained preserved (Fig. 6). The lumens of a large part of the excretory tubules remained dilated, containing fragments of cell membranes.

Discussion

Undoubtedly, the involvement of each organ in the realization of the consequences of local ischemia-reperfusion has its own characteristics and is now being actively studied by scientists in all around the world. In the conditions of wide variety of types of operations, tourniquet is actively used in arthroplasty [17], before restoration of blood supply to internal organs or limbs after transplantation [16]. And a special place among them is occupied by ischemia-reperfusion of the limb due to the use of hemostatic tourniquet in combat injuries [12].

Applying a tourniquet to any part of the body - whether in surgery on the heart or a wounded vessel of the limb, and release from it has a number of similar pathogenetic mechanisms. This is hypoxia of the tissue due to stop of its normal blood supply [24], the pressure of the tourniquet on the vessel (ligature) or subordinate tissues, so the complications, respectively, are both local and remote [6, 23]. Due to the bleeding of this area, hypoxia develops first with following generation of reactive oxygen species [7]. This causes "oxidative stress" as a manifestation of an imbalance between antioxidant defense systems and the activity of oxidants. Thus, based on the fact that in the reperfusion syndrome there are two stages - the local response, which follows the reperfusion and is manifested by swelling of the limb, followed by the development of local damage; and systemic damage, which is manifested by multiorgan affection. Physiological and anatomical studies confirm that the most brightly changes, in particular irreversible damage to muscle cells, begin after 3 hours of ischemia [3] and expressed as microvascular damage. At local compression of tissues of an extremity with a hemostatic tourniquet muscle damage appear. After that accumulation of myoglobin in plasma eventually becomes one of the factors causing toxic

necrosis of tubular epithelium, provoking development of myoglobinuric nephrosis and acute renal failure which, as usual, up to the 9-12th day results in the restoration of renal function [20].

The intensity of the inflammatory response has both local and systemic effects, which are a consequence of pathophysiological, biochemical and immunological changes that occur in ischemic-reperfusion periods. And despite the fact that there are certain features of the development of consequences in the heart, brain, extremities in diabetes or organs after transplantation or use of hemostatic jute, but the essence of the mechanisms remains the same: [8] active oxygen and active neutrophils are one of the main effectors, responsible for the development of local and systemic damage. A paradox is realized in the mechanism of reperfusion injury: the lack of oxygen is detrimental to the normal functioning of cells. Reperfusion, instead of normalizing metabolism, initiates an inflammatory response that can either enhance the local tissue response or stop further organ damage. Polymorphonuclear neutrophils that migrate to distant organs due to ischemia-reperfusion release lipid mediators, including leukotriene B4, cysteinyl-LTs, platelet activating factor that triggers inflammation in response [2].

Thus, summarizing the written above, the cellular damage that occurs in the reperfusion phase may be either a consequence of cell damage that has already occurred in the ischemic stage, or a consequence of the inflammatory response. Intracellular damage - in part may be the same as oxygen-free cell damage. In addition, activation of intracellular signaling cascades and apoptotic mechanisms is commonly discussed [5, 21].

Conclusions

Comparison of groups depending on the severity showed that both the isolated use of a tourniquet and massive blood loss had long-term, systemic consequences, however, more expressed in EG-2. The main changes consisted of heterogeneous blood supply in small and medium-sized vessels; single vascular glomeruli shrunken, endothelial cells of arterioles were slightly damaged. On the 7th and 14th days changes in the structure of EG-1 were mostly absent, although in EG-2 the epitheliocytes of the outer layer of the capsule remained flattened, retained full blood vessels of the venous bed in the interstitium, and the vast majority of epitheliocytes of the excretory tubules were at different stages of hydropic dystrophy with partly desquamation of the epithelium into the gaps of the tubules. Also, the basal membranes of the tubules were not completely visualized, which indicates deep damage in the structures caused by acute ischemia next to the bleeding.

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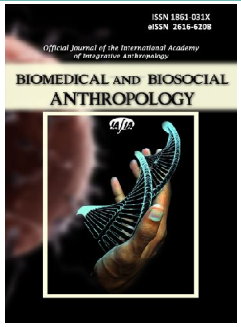

Comparative assessment of renal function by cystatin C level in patients with hypertension and extrasystole

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Although the tight connection of the cardiovascular system and the kidneys is well known, using of cystatin C (Cys-C) opens new horizons in studying early renal failure stages. The study aimed to compare the functional status of the kidneys in patients with hypertension and extrasystole to the level of Cys-C. 156 patients with stage II hypertension (EH II) were examined. 124 of them had frequent symptomatic extrasystoles (74 - of supraventricular origin and 50 - ventricular), 32 patients had no arrhythmias, and were referred to the comparison group. The control group consisted of 30 healthy people with normal blood pressure (BP). All patients underwent a complete clinical examination, blood pressure measurement, daily blood pressure monitoring, daily electrocardiogram monitoring, echocardiography, and determination of renal function (creatinine, blood electrolytes, serum cystatin C) followed by calculation of glomerular filtration rate (GFR). The level of Cys-C in patients with hypertension was significantly higher ($p<0.001$) compared with healthy individuals. Among patients with arrhythmias, the highest level of Cys-C was noted in patients with ventricular arrhythmias. The correlation analysis showed that the level of Cys-C was higher in the presence of frequent extrasystoles (namely of ventricular origin), smoking, high blood pressure, increased systolic and pulse blood pressure, the presence of concentric left ventricular hypertrophy, dyslipidemia, increased creatinine level and decreased GFR. All three EH II patient groups had significantly lower GFR (calculated by creatinine level) ($p<0.001$). The lowest creatinine-based GFR was revealed in patients with ventricular extrasystole. All patients with EH II had significantly lower Cys-C based GFR than the control group ($p<0.001$). Mean Cys-C-based GFR values in patients with extrasystole were significantly lower than in patients without extrasystole ($p<0.03$). The analysis of GFR levels depending on the extrasystole origin was provided. The lowest level of GFR was recorded in patients with ventricular extrasystole. It was significantly different from the patients with supraventricular extrasystole ($p=0.02$). Our findings confirm the opinion of other researchers that Cys-C is an early marker of renal dysfunction in patients with hypertension, which is more sensitive than creatinine. Another finding is that ventricular extrasystole is more hemodynamically and metabolically unfavorable compared to supraventricular based on clinical and prognostic evaluation.

Keywords: *cystatin C, creatinine, glomerular filtration rate, essential hypertension, supraventricular extrasystole, ventricular extrasystole.*

Introduction

It is currently unknown how various forms of cardiac arrhythmias, including extrasystoles, affect the state of renal function in patients with essential hypertension. However, there is a lot of evidence that risk factors such as obesity, metabolic syndrome, hypertension, burden of cardiovascular history, type 2 diabetes, as well as the activation of inflammation, oxidative stress, and the renin-angiotensin-aldosterone mechanism are common for atrial fibrillation and renal dysfunction [4, 17, 20, 24]. A large number of studies aimed at studying the relationship between atrial fibrillation and renal dysfunction proved that not only renal dysfunction is a predictor of arrhythmias, but also the presence of arrhythmia is associated with an increased likelihood of further GFR decrease and increase of albuminuria due to deterioration of systemic and intrarenal hemodynamics. However, our knowledge about

early markers of renal dysfunction in patients with EH and concomitant extrasystole is incomplete and requires further specification [1, 2, 18, 22, 23].

The estimation of GFR is common in clinical practice for the assessment of the functional status of the kidneys, but its reduction occurs only when the number of functioning nephrons decreases, so it cannot serve as an early marker of kidney damage. This is a prerequisite for searching for more sensitive diagnostic methods [10, 14, 19].

Cys-C is the earliest and most informative marker of renal dysfunction, according to the KDIGO 2012 guidelines [21]. Cys-C is a basic peptide consisting of 122 amino acid residues with a molecular weight of about 13 kDa. It is an important extracellular inhibitor of cysteine proteases, which belong to the second type of cystatin superfamily. The active and mature form of Cys-C in humans is called the Cys-C monomer and consists of a single non-glycosylated polypeptide chain, the individual links of which are interconnected by disulfide bridges. The Cys-C monomer is present in almost all body fluids, but the largest amount is found in cerebrospinal fluid, milk, and semen. The level of this peptide can also be determined in urine and saliva [3, 7, 25].

Cys-C is freely filtered through the glomerular membrane due to its low molecular weight. Due to this, the level of Cys-C is relatively stable in the systemic circulation. It is a more sensitive marker of GFR reduction than creatinine because it could not be affected by factors such as age, gender, muscle mass, diet, physical activity, and race. It serves as an effective marker for early detection of renal failure, even at normal creatinine levels [16, 23].

The study aimed to compare the functional state of the kidneys in patients with hypertension and extrasystole based on the level of Cys-C.

Materials and methods

The study involved 156 patients with essential hypertension stage II (EH II). 124 of them (aged 27 to 75 years) had frequent symptomatic extrasystoles and formed the main clinical array of the study. 32 patients with EH II, but without cardiac arrhythmias (aged 32 to 72 years) were the comparison group. Among patients of the main array, 50 (40.3 %) were males and 74 (59.6 %) - females. The comparison group included 15 (46.9 %) men and 17 (53.1 %) women. Aside from that, 30 relatively healthy, normal people were assigned to the control group, which included 16 (53.3 %) men and 14 (46.7 %) women. The statistical analysis between the main group, comparison and control groups showed no significant differences ($p>0.05$) by age and sex, which indicated their age and sex homogeneity.

74 (59.7 %) of 124 patients with EH II and concomitant frequent extrasystoles had supraventricular (SVE) and 50 (40.3 %) had ventricular extrasystoles. Their arrhythmic history ranged from 1 to 27 years and averaged 8.062 ± 0.421 years.

Before participating in the study, all patients signed an informed consent form in accordance with the Declaration of Helsinki and the International Code of Medical Ethics.

All patients were examined in a complete, comprehensive clinical, laboratory, and instrumental examination, including the assessment of renal function, aiming to establish the underlying diagnosis and comorbidities before they entered the study.

Those who agreed to participate in the study were examined using the following methods: 1) general clinical and anthropometric examination, measurement of blood pressure (BP); 2) ECG with12 leads, daily ECG monitoring, daily blood pressure monitoring, echocardiography; 3) assessment of the functional state of the kidneys. The general clinical examination included the analysis of medical history, the establishment of the main and concomitant diagnosis, and the assessment of the inclusion-exclusion criteria. Then, patients were referred to the appropriate group.

Blood pressure was measured according to the recommendations of the Ukrainian Society of Cardiology (2013) using a sphygmomanometer (Microlife, Switzerland).

Electrocardiography in 12 leads was performed according to the standard method on an ECG device "UKARD" (Hungary).

Daily blood pressure monitoring (DBPM) and Holter ECG monitoring (HM ECG) were performed using the equipment "DiaCard" (JSC "Solvaig", Ukraine) according to the standard protocol.

Assessment of the structural and functional state of the heart was performed using an echocardiograph "My Lab 25" (Italy) in one- and two-dimensional modes with color, pulse and continuous-wave Doppler.

Assessment of the functional state of the kidneys was performed using the following tests: 1) the level of blood electrolytes (potassium and sodium) in mmol/l was determined by an ion-selective method using an electrolyte analyzer Easystat (USA); 2) blood creatinine level in μmol/l using the kinetically modified Jaffa method on a Cobas 6000 analyzer (with 501 modules) using the Roche Diagnostics test system (Switzerland). It should be noted that the study included only patients with a creatinine level which exceeded the reference values - 62-115 μmol/l in men and 53-97 μmol/l in women); 3) the serum level of Cys-C (ng/ml) was determined by an enzyme-linked immunosorbent assay using the "Human Cystatin C" set (BioVendor, Czech Republic, Lot: E18-091P01); 4) the glomerular filtration rate in ml/min /1.73 m^2 was calculated according to CKD-EPI formulas using online calculators: https://boris.bikbov.ru/2013/07/21/kalkulyator-skf-rascheta-skorosti-klubochkovoy- filtratsii (for creatinine) and https://medlabdiag.ru/calculators/clearance_cys (for Cys-C).

Statistical processing of the study results was performed using the software "Statistica" v. 12.0 (StatSoft) according to the recommendations for processing medical and biological research. The results were presented as a

value of median and quartile with an indication of 25 and 75 percentile, and as a percent (%) - for relative values. Comparison of relative values (%) was performed using the criterion χ^2. Absolute values were compared by the Kruskal-Wallis ANOVA test & the Median test. Spearman's rank correlation analysis was used to determine the relationship between certain parameters [11].

Results

The method of variation statistics was used to determine the variation of serum Cys-C level in the general sample, in patients of different clinical groups and in practically healthy normotensive individuals (Fig. 1). In patients with EH, the level of Cys-C was significantly higher ($p<0.001$) compared with healthy individuals. The average value of Cys-C in all patients with EH was 1.162 (1.003; 1.371) mg/l, which was 23.3 % ($p<0.001$) higher than the corresponding level in healthy people. In a more detailed analysis, it was found that the average levels of Cys-C in patients with EH without arrhythmias were lower than in patients with EH and extrasystole. Among the patients with arrhythmias, the highest level of Cys-C was recorded in patients with frequent VE, which was significantly different from the corresponding level of Cys-C in patients with SVE (1.254 (1.101; 1.384) mg/l vs. 1.143 (1.000; 1.384) mg/l, $p<0.05$), patients without arrhythmias (1.254 (1.101; 1.384) mg/l vs. 1.011 (0.857; 1.237) mg/ml, $p<0.001$) and healthy individuals (1.254 (1.101; 1.384) mg/l vs. 0.892 (0.631; 1.043) mg/l, respectively, $p<0.001$).

The significance of intergroup differences in the level of Cys-C serum calculated by Kruskal-Wallis ANOVA test & Median test is shown in table 1.

In addition, we performed a Spearman Rank Order Correlation between Cys-C levels and various clinical, instrumental, and laboratory parameters (Table 2).

The results of Spearman's rank correlation analysis showed (see Table 2) that the serum Cys-C level demonstrated significant direct correlations with the

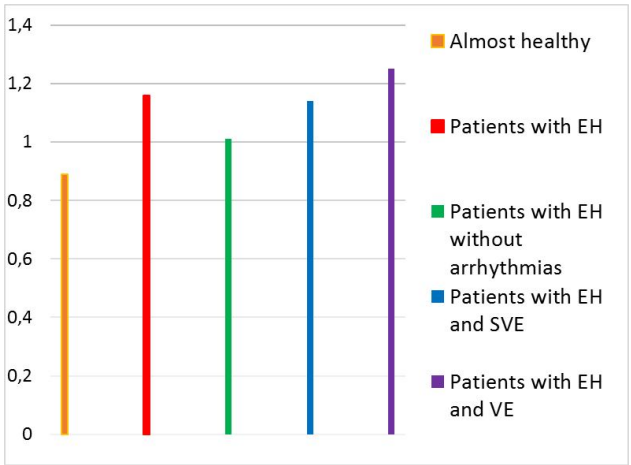

Fig. 1. Serum Cys-C level (in mg/l) in different clinical groups of patients.

Table 1. Differences in serum Cys-C levels between different clinical groups of patients.

Groups	1	2	3	4	5
1		<0.001	<0.05	<0.001	<0.001
2	<0.001		<0.01	>0.05	>0.05
3	<0.05	<0.01		<0.05	<0.001
4	<0.001	>0.05	<0.05		<0.05
5	<0.001	>0.05	<0.001	<0.05	

Notes: 1 - healthy individuals (n=30); 2 - all patients with EH (n=156); 3 - patients with EH without arrhythmia (n=32); 4 - patients with EH with SVE (n=74); 5 - patients with EH with VE (n=50).

Table 2. Significant associative correlations of Cys-C level with various clinical-instrumental and laboratory parameters (Spearman's rank order correlations).

Clinical, instrumental and laboratory parameters	Spearmen R	p-value
Presence of frequent extrasystole, points (1 - yes, 0 - no)	0.288	0.0003
Presence of frequent VE, points (1 - yes, 0 - no)	0.381	0.0001
Sex (1 - male, 0 - female)	-0.229	0.0041
High grade (III) EH, points (1 - yes, 0 - no)	0.312	0.0001
Smoking (1 - yes, 0 - no)	0.264	0.0009
SBPn, mm Hg (by ABPM data)	0.242	0.0221
PBP, mm Hg (by ABPM data)	0.344	0.0001
SBP ERV, mm Hg (by ABPM data)	0.266	0.0100
LVMI, g/m^2 (by EchoCG)	0.307	0.0007
RWT (by EchoCG)	0.284	0.0012
Concentric LV hypertrophy by Ganau, points (1 - yes, 0 - no) (by EchoCG)	0.299	0.0013
Number of VE (by ECG HM)	0.425	0.0001
Presence of paired VE, (1 - yes, 0 - no) (by ECG HM)	0.511	0.0001
Number of paired VE (by ECG HM)	0.402	0.0001
LDL-C, mmol/l	0.271	0.0003
AR, units	0.174	0.0222
Creatinine, mcmol/l	0.627	0.0001
GFR by CKD-EPI, ml/min/1.73 m^2	0.632	0.0001

Notes: VE - ventricular extrasystole, EH - essential hypertension, SBPn - mean night systolic blood pressure, PBPn - mean night pulse blood pressure, SBP ERV - Systolic blood pressure early rise velocity, LVMI - left venricular mass index, RWT - relative wall thickness, EchoCG - echocardiography, ECG HM - ECG Holter monitoring, LDL-C - low density lipoprotein cholesterol, AR - atherogenic ratio, GFR - glomerular filtration rate.

presence of frequent extrasystoles, regardless of their origin (r=0.29), with the presence of a ventricular extrasystole (r=0.38), high (III) degree of EH (r=0.31), smoking (r=0.26), mean night SBP and PBP (r=0.24 and r=0.34), rate of early rise of SBP (r=0.27), LVMI (r=0.31), relative myocardial wall thickness (r=0.28), presence of concentric LV hypertrophy (r=0.30), total number of VE

Table 3. Functional status of the kidneys in patients with hypertension and different origin of extrasystole (median (25.0th percentl; 75.0th percentl), or n (%)).

Functional parameters of kidneys	Patients without extrasystole	Patients with EH and SVE	Patients with EH and VE	p
	Group 1 (n=32)	Group 2 (n=74)	Group 3 (n=50)	
Creatinine, mcmol/l	74.24 (58.37; 97.13)	85.02 (78.34; 92.11)*	89.33 (82.01; 94.07)*	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
Potassium, mmol/l	4.333 (4.09; 4.52)	4.209 (4.001; 4.333)	4.175 (4.022; 4.300)	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
Natrium, mmol/l	139.2 (138.1; 141.4)	142.3 (138.3; 145.4)	141.1 (139.0; 145.3)	**$p_{1-2}<0.05$** **$p_{1-3}<0.05$** $p_{2-3}>0.05$
(K/Na)*100	3.091 (2.864; 3.262)	2.922 (2.802; 3.083)*	2.922 (2.831; 3.052)*	**$p_{1-2}<0.05$** **$p_{1-3}<0.05$** $p_{2-3}>0.05$
GFR by CKD-EPI, ml/min/1.73 m^2	64.02 (42.17; 87.08)***	53.25 (46.34; 67.09)***	50.12 (44.24; 60.05)***	$p_{1-2}>0.05$ **$p_{1-3}<0.05$** $p_{2-3}>0.05$
GFR < 90 ml/min/1.73 m^2	26 (81.3 %)	72 (97.3 %)	49 (98.0 %)	**$p_{1-2}<0.01$** **$p_{1-3}<0.01$** $p_{2-3}>0.05$
GFR < 60 ml/min/1.73 m^2	13 (40.6 %)	47 (63.5 %)	37 (74.0 %)	**$p_{1-2}<0.05$** **$p_{1-3}<0.01$** $p_{2-3}>0.05$
GFR < 45 ml/min/1.73 m^2	9 (28.1 %)	15 (20.3 %)	15 (30.0 %)	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
Cys-C, mg/l	1.011 (0.857; 1.237)*	1.143 (1.000; 1.384)**	1.254 (1.101; 1.384)***	**$p_{1-2}<0.05$** **$p_{1-3}<0.001$** **$p_{2-3}<0.05$**
GFR by Cys-C, ml/min/1.73 m^2	74.12 (55.01; 94.21)***	63.11 (51.07; 74.23)***	54.17 (48.05; 65.22)***	**$p_{1-2}<0.05$** **$p_{1-3}<0.01$** **$p_{2-3}<0.05$**
GFR < 90 ml/min/1.73 m^2	23 (71.9 %)	68 (91.9 %)	48 (96.0 %)	**$p_{1-2}<0,01$** **$p_{1-3}<0.01$** $p_{2-3}>0.05$
GFR < 60 ml/min/1.73 m^2	10 (31.3 %)	31 (41.9 %)	32 (64.0 %)	$p_{1-2}>0.05$ **$p_{1-3}<0.01$** **$p_{2-3}<0.05$**
GFR < 45 ml/min/1.73 m^2	2 (6.3 %)	11 (14.9 %)	8 (16.0 %)	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$

Notes: intergroup significance of absolute differences calculated by Kruskal-Wallis ANOVA test & Median test and percentages - by criterion χ^2; GFR - glomerular filtration rate; signs *, ** or *** indicate the significance of the difference compared with the control group (n = 30), at levels of <0.05, <0.01 and <0.001, respectively.

(r=0.43), the presence of paired VE (r=0.51), total number of paired VE (r=0.40), LDL cholesterol (r=0.27), atherogenic rate (r=0.17), creatinine (r=0.63) and glomerular filtration rate by CKD-EPI (r=0.63). At the same time, a significant inverse correlation was found between the level of Cys-C and the male sex (r= -0.23).

To assess the functional state of the kidneys, we determined the level of cystatin C and calculated GFR by the level of Cys-C (adapted formula CKD-EPI) in addition to routine determination of electrolytes, creatinine and calculation of GFR by the formula CKD-EPI (online calculator), (Table 3) [5, 13].

Analysis of the data showed that the average creatinine level in patients with extrasystole did not exceed the reference values and differed significantly only compared with healthy individuals (85.02 μmol/l in patients with SVE and 89.33 μmol/l in patients with VE versus 70.08 μmol/l, p<0.05). Patients with extrasystole had higher sodium levels than patients without extrasystole (142.3 mmol/l in patients with SVE and 141.1 mmol/l in patients with VE versus 139.2 mmol/l, p<0.05). The level of sodium in patients of the control group was 140.4 mmol/l, and had no significant difference

compared with patients in the clinical array and the comparison group. The rate (K/Na)*100 in patients with extrasystole was significantly lower than in patients without arrhythmia (2.922 vs. 3.091 p<0.05) and practically healthy individuals (2.922 vs. 3.082, p<0.05). GFR (creatinine-based) in all 3 groups of patients with EH was significantly lower than in healthy individuals (64.02 ml/min/1.73 m^2 in patients without extrasystole, 53.25 ml/min/1.73 m^2 in patients with SVE and 50.12 ml/min/1.73 m^2 in patients with SE against 91.12 ml/min/1.73 m^2, respectively, p<0.001). The lowest GFR (calculated by creatinine) was revealed in patients with VE. It differed significantly from patients without extrasystoles (50.12 vs. 64.02 ml/min/1.73 m^2, p<0.05). The distribution of patients by GFR showed that 98.0 % of patients with VE and 97.3 % of patients with SVE had a GFR of less than 90 ml/min/1.73 m^2, which was significantly different from patients without arrhythmias (81.3 %; p<0.01). The level of GFR of less than 60 ml/min/1.73 m^2 was found in 74.0 % of patients with VE and in 63.5 % of patients with SVE. It was statistically different from patients without extrasystole (40.6 %, p<0.05). The level of GFR of less than 45 ml/min /1.73 m2 was determined in 28.1 % of patients in the comparison group, in 20.3 % of patients with EH and SVE, and in 30.0 % of patients with EH and VE. There were no statistically significant differences between groups. The mean level of Cys-C in patients with frequent extrasystoles was significantly higher compared with patients without arrhythmias (p<0.05) and healthy individuals (p<0.01) (see Fig. 1). At the same time, the highest level of Cys-C was noted in patients with a VE, which was significantly different from patients with SVE (1.254 vs. 1.143 mg/l, p<0.05) and patients without extrasystole (1,011 mg/l, p<0.001). It was noted that the average values of GFR calculated by Cys-C were higher than the corresponding values of GFR calculated by creatinine. GFR by Cys-C in all patients with EH was significantly lower than in the control group (74.12 ml/min/1.73 m^2 in patients without extrasystole, 63.11 ml/min/1.73 m^2 in patients with SVE and 54.17 ml/min/1.73 m^2 in patients with VE against 94.08 ml/min/1.73 m^2, respectively, p<0.001). Mean GFR values calculated by Cys-C in patients with extrasystole were significantly lower than in patients without extrasystole (54.17 ml/min/1.73 m^2 in patients with VE and 63.11 ml/min/1.73 m^2 in patients with SVE versus 74.12 ml/min/1.73 m^2, p<0.05). Analysis of GFR levels depending on the place of extrasystole's origin showed the lowest GFR level in patients with VE. It differed significantly from patients with SVE (54.17 vs. 63.11 ml/min/1.73 m^2, p <0.05). GFR of less than 90 ml/min/1.73 m^2 was met in 96.0 % of patients with VE and in 91.9 % of those with SVE, while in the comparison group it was significantly rarer (71.9 %; p<0.01). The highest percentage of patients with GFR of less than 60 ml/min/1.73 m^2 was found in patients with frequent VE, and it differed significantly from patients with SVE and without arrhythmias (64.0 % vs. 41.9 % and vs. 31.3 %, p<0.05). A GFR of less than 45 ml/min/1.73 m2 was met in 6.3 % of patients in the comparison group, in 14.9 % of patients with SVE, and in 16.0 % of patients with VE. The differences between them were non-significant (see Table 3).

Discussion

The tight connection between the cardiovascular system and the kidneys is well known. Their relationships are multifaceted and work as a kind of feedback. In this context, the kidney can play a role of target organ, but also take an active part in the formation of systemic metabolic and vascular pathological processes. Dysfunction of any link leads to activation of the renin-angiotensin-aldosterone system and sympathetic hyperactivation, the development of endothelial dysfunction and chronic systemic inflammation. Thus, a complex pathogenic cycle is closed, leading to the progression of heart and kidney dysfunction, remodeling of the myocardium and vascular wall, increased morbidity and mortality. This pathophysiological mechanism in modern medicine is called the cardiorenal continuum [7, 8, 9].

In this context, GFR plays an important role. Its reduction should be considered as an independent risk factor for the progression of cardiovascular pathology and cardiovascular mortality [2, 12]. A series of large population-based studies have shown that even an initial decrease in renal function with serum creatinine levels within normal limits or slightly elevated, is accompanied by a tremendous increase in cardiovascular morbidity and mortality [13, 14, 16]. A lot of studies have confirmed that the deterioration of the functional state of the kidneys in patients with hypertension is associated with a poor cardiovascular prognosis [15, 21, 22, 23]. Such conclusions prompted researchers to identify and study in detail early markers of renal dysfunction, in particular Cys-C.

We determined and compared the average level of Cys-C in patients with stage II EH without cardiac arrhythmias, in patients with EH and frequent extrasystoles, taking into account their supraventricular or ventricular origin. We did a detailed analysis of the relationship between serum Cys-C levels and different clinical and instrumental and laboratory parameters in this cohort of patients, as well as a comparative assessment of the functional status of the kidneys based on Cys-C and creatinine serum levels. The average level of Cys-C in patients with EH II was significantly higher than in healthy individuals (p<0.001). Mean Cys-C levels in patients with EH and extrasystoles were higher than in patients with EH but without arrhythmias (p<0.05). The level of Cys-C was the highest in patients with frequent VE among all patients with arrhythmias. It was significantly different from the corresponding level of Cys-C in patients with SVE (p<0.05), patients without arrhythmias (p<0.001), and healthy people (p<0.001). EH and extrasystole (especially the ventricular) are known contributors to heart remodeling and dysfunction. It is known that heart remodeling is accompanied by certain inflammatory changes (apoptosis, atrial fibrosis, disorders of calcium transfer and regulation of connexin, etc.) [2, 4, 6].

Cys-C is frequently referred to as an inflammatory marker because it is produced during inflammation by cells containing the nucleus [2, 6], which may explain why the level of this peptide is higher in patients with hypertension and extrasystole.

Spriman's correlation analysis revealed an association between Cys-C levels and the following parameters: the presence of frequent extrasystoles (in particular VE and paired VE), frequency of VE per 1 hour, the total number of paired VE, smoking, high grade of blood pressure, elevated means of night SBP and PBP, early SBP rise, LVMI, RWT, presence of LV concentric hypertrophy, increased LDL and atherogenic ratio, increased creatinine and decreased GFR. It suggests the existence of common pathophysiological mechanisms between increasing levels of Cys-C, known risk factors, and cardiovascular diseases. Our data confirms the point of view that Cys-C is currently the "gold standard" and prognostic marker that determines kidney function [3, 19, 21] and simultaneously serves as an additional indicator of cardiovascular risk.

The average creatinine level in patients with EH and extrasystole was significantly higher when compared to healthy individuals. The presence of frequent extrasystoles in patients with stage II EH was associated with an increased cystatin C and serum sodium level, a decrease in the K/Na ratio, and a decrease in the GFR determined by Cys-C. In addition, all patients were ranged depending on the meaning of GFR, because a number of meta-analyses have identified a critical level of GFR associated with the increase in cardiovascular risk and overall mortality, which is approximately equal to 75 ml/min/1.73 m^2 [3, 12, 13, 15, 16]. In addition, all patients were ranged depending on the meaning of GFR, taking into account that some meta-analyses identified a critical level of GFR approximately equal to 75 ml/min/1.73 m^2, which was associated with an increase in cardiovascular risk and overall mortality [3, 12, 13, 15, 16]. In patients with stage II EH, the presence of a VE was associated with the highest level of Cys-C, a decrease in GFR (both creatinine and cystatin-C based), and an increase in the number of patients with Cys-C based GFR of less than 60 ml/min/1.73 m^2. The mean GFR values calculated by Cys-C were higher than the corresponding values of GFR calculated by creatinine. It is known that Cys-C today is used as a more accurate and sensitive marker of renal dysfunction than creatinine [12, 15].

Our study suggests that patients with stage II EH had a decrease in GFR compared with healthy individuals. In turn, the lowest GFR (both creatinine and Cys-C based) was found in patients with stage II EH and frequent VE. Some authors have described more severe hemodynamic and metabolic disorders in the case of ventricular extrasystole. It might be a suitable explanation of our results, but it needs further study. [1, 4, 20].

In the future, it is advisable to provide a deeper investigation of the Cys-C properties in patients with hypertension and various comorbid conditions, and other cardiovascular diseases. The implementation of diagnostic methods based on this marker requires re-equipment of laboratories, training of laboratory personnel and physicians to calculate Cys-C-based GFR, but it may improve the diagnosis and stratification of cardiovascular risk in our country.

Conclusions

1. The level of Cys-C was significantly higher in patients with EH, compared to the control ($p<0.001$), while in the presence of extrasystole, the mean level of Cys-C was significantly higher than in patients without extrasystoles ($p<0.05$). The highest level of Cys-C was found in patients with EH and VE. It differed significantly from the corresponding level of Cys-C in patients with SVE ($p<0.05$), patients without arrhythmias ($p<0.001$), and healthy persons ($p<0.001$).

2. Spearman's correlation analysis revealed a direct relationship between Cys-C levels and frequent extrasystole, in particular of ventricular origin (presence of frequent VE, frequency of VE per 1 h, presence of paired VE, and the total number of paired VE per day), known cardiovascular risk factors, such as smoking and a high degree of hypertension, some indicators of DBPM (mean night SBP, PBP, early SBP rise), concentric LV hypertrophy, LVMI and RWT, metabolic risk factors (LDL cholesterol, AR) and indicators of renal function (creatinine and GFR). These results prove the ability to use Cys-C as a prognostic marker of renal dysfunction and increased cardiovascular risk in patients with hypertension.

3. In patients with stage II EH, the presence of frequent extrasystoles is associated with an increase in Cys-C, sodium, decreased potassium to sodium ratio, decreased renal filtration function, as determined by Cys-C-based GFR, and an increase in the number of patients with GFR of less than 90 (for creatinine and Cys-C-based) and less than 60 ml/min/1.73 m^2 (for creatinine-based). In patients with stage II EH, the presence of VE is associated with the highest level of Cys-C, a decrease in GFR (both creatinine- and Cys-C-based) and an increase in the number of patients with Cys-C-based GFR of less than 60 ml/min/1.73 m^2.

4. In patients with stage II EH there is a decrease in GFR, compared with healthy individuals. The lowest GFR (both creatinine- and Cys-C-based) was reported in patients with stage II EH and frequent VE. It allows to consider extrasystole of the ventricular origin as more hemodynamically and metabolically unfavorable than supraventricular and to use it as an important clinical marker of metabolic disorders.

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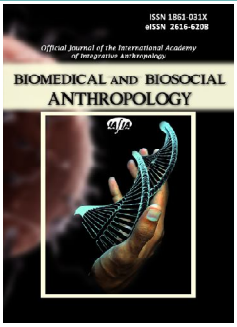

Determination of cephalometric parameters, which usually do not change during surgical and orthodontic treatment depending on facial types according to Garson in Ukrainian young men and young women with orthognathic occlusion

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Aesthetics is one of the key elements that accompanies modern medicine, in particular, dentistry. The need for treatment not only eliminates the symptoms of the disease but also leads to the restoration or improvement of the aesthetic appearance of the person, and especially the face, gave impetus to the development of new areas of science and technology. An important step in the implementation of such treatments is experimental research to identify the norm for certain categories of the population, primarily according to sex and ethnic group. The aim of the study was to establish the characteristics of cephalometric parameters in Ukrainian young men and young women with orthognathic occlusion, which usually do not change during surgical and orthodontic treatment, depending on sex and facial types according to Garson. On the basis of the clinic "Vinintermed" teleroentgenography was performed using a dental cone-beam tomograph Veraviewepocs 3D Morita (Japan). Cephalometric examination of lateral teleroentgenograms in 46 young men (aged 17 to 21 years) and 72 young women (aged 16 to 20 years) with orthognathic occlusion was done. The type of face was determined according to the morphological index of Garson. The evaluation of parameters that usually do not change during surgical and orthodontic treatment was performed in the licensed package "Statistica 6.0" using non-parametric methods of evaluation of the results. The percentile ranges of cephalometric parameters, which usually do not change during surgical and orthodontic treatment depending on the facial types of Ukrainian young men and young women with orthognathic occlusion has been established. Pronounced manifestations of sexual dimorphism of cephalometric parameters, which usually do not change during surgical and orthodontic treatment (higher values in young men) are established only for most linear dimensions (values of distances NS, Ar-Go, N-Se, N-CC, P-PTV and S-Ar) in representatives of different types of faces. Both between young men and young women with different face types, there are almost no reliable or tendencies of differences in cephalometric parameters, which usually do not change during surgical and orthodontic treatment.

Keywords: *teleroentgenography, cephalometry, young men, young women, face types, orthognathic occlusion.*

Introduction

One of the key issues in orthodontics, which has become relevant in recent decades, is the study of the variability of facial features, skull structure and their relationship to the position of the teeth among members of a particular ethnic group.

Thus, researchers working in this direction are already aware of the existence of works where the data on the specificity of the above indicators among different nationalities are confirmed. 127 ethnic Moroccans underwent teleroentgenography to identify the relationships between cephalometric and odontometric parameters. Statistical analysis of the obtained data revealed the existence of correlations between the upper posterior alveolar height and the anterior height of the face, the

posterior height of the face. The lower anterior alveolar height at the same time is negatively correlated with the face height index [1].

For residents of western Ukraine, the existence of reliable correlations of medium strength between the linear dimensions of molars (parietal-lingual and mesio-distal dimensions) and indicators of the skull. With the indicators of the facial skull, the largest number of reliable and medium correlations with the height of teeth, crowns, root length, parietal-lingual and mesio-distal dimensions of molars [12]. A similar study, however, conducted with the population of southern Ukraine, found correlations between most sizes of molars on the lower jaw and the length and height of the nose [24].

Indian scientists have identified the size of the brain and facial skull for residents of Gujarat. The control group was residents of other Indian states. It was found that the standard deviation of the main and front index for residents of the state was 5.3345 and 6.0040, and for residents of other states - 7.3472 and 6.0525, respectively. Most people in Gujarat were mesocephalic and dolichocephalic, while people in other states were dolichocephalic and brachycephalic [22].

Manifestations of sexual dimorphism in the features of cephalometric and odontometric indicators were revealed for the people of Korea. The height of the anterior alveolar process of the upper jaw correlated with the deviation of the upper incisor; moreover, higher power correlations were found in women compared to men [13].

A comparative analysis of cephalometric and odontometric parameters between the populations of Japan and Bangladesh found that the inhabitants of the latter are characterized by lower face height ($p<0.01$), higher indicators of the position of the upper and lower jaws ($p<0.01$) compared with the population of Japan [2].

In another study, an analysis of data from mainland Japan and the Ryukyu Islands found that women from the island of Japan had smaller mandibular incisor, less depth of the upper lip, and an inclined to the front mandibular symphysis [26].

In addition to identifying the ethnic characteristics of odontometric and cephalometric indicators, an important component of the study is to identify the overall relationships and effects of one component on another and vice versa, the strength of these relationships and their direction, etc. [7, 8].

A group of researchers from Ukraine and India [10] by regression analysis built reliable models to determine the characteristics of the position of the central incisors of the upper and lower jaw according to the Steiner method. The study confirmed the existence of a relationship between the angle ANB and the angles Max1_NA and Max1_SN and the distance 1u_NA.

However, it is also worth paying attention to the method of obtaining data on the features of cephalometric parameters of both the cranial and facial parts of the skull. Thus, some works indicate that the photometric method can be successfully used for research and is almost not inferior to traditional methods when it is necessary to use a centimeter tape [17, 21].

Regarding teleroentgenographic measurements, there are also discussions about the choice of the best cephalometric method of research. In the work of Paranhos L. R. and co-authors [18], the use of the SN-GoGn angle is preferred according to the results.

Similar data were obtained by Brazilian researchers during the analysis of 95 teleroentgenograms of 54 men and 41 women aged 15-21 years. Kappa was considered valid for the cephalometric evaluation method for Jarabak SN-GoGn (0.06 and 36.8 %) [9].

It is obvious that the question of studying the relationship between cephalometric indicators, face type, odontometric indicators has not yet been resolved. Work on data collection for representatives of different ethnic groups continues in different parts of the world [11, 23, 25].

Given the above data, there is a need to conduct a study of cephalometric parameters in the Ukrainian population, taking into account sex, type of bite and face type.

The aim of the study was to establish the characteristics of cephalometric parameters in Ukrainian young men and young women with orthognathic occlusion, which usually do not change during surgical and orthodontic treatment, depending on sex and facial types according to Garson.

Materials and methods

On the basis of the clinic "Winintermed" teleroentgenography was performed using a dental cone-beam tomograph Veraviewepocs 3D Morita (Japan) in the mode of cephalometric examination of 8 young men (aged 17 to 21 years) and 17 young women (aged 16 to 20 years) who had physiological bite as close as possible to the orthognathic (hereinafter orthognathic) which is determined by 11 points according to Bushan M. G. and others [3]. Cephalometric analysis was performed using OnyxCeph^{3}™ software, 3DPro version, Image Instruments GmbH, Germany (№ URSQ-1799 software license). From the database of the research center of National Pirogov Memorial Medical University, Vinnytsya selected 38 young men and 55 young women of the same age with orthognathic occlusion, who also underwent teleroentgenography followed by cephalometric analysis.

Committee on Bioethics of National Pirogov Memorial Medical University, Vinnytsya (protocol № 9 from 21.11.2019) it was established that the conducted research meets the bioethical and moral and legal requirements of the Declaration of Helsinki, the Convention of the Council of Europe on human rights and biomedicine (1977), the relevant provisions of the WHO and the laws of Ukraine according to the order of the Ministry of Health of Ukraine № 281 from 01.11.2000.

The type of face was determined according to the morphological index of Garson (Fig. 1) according to the

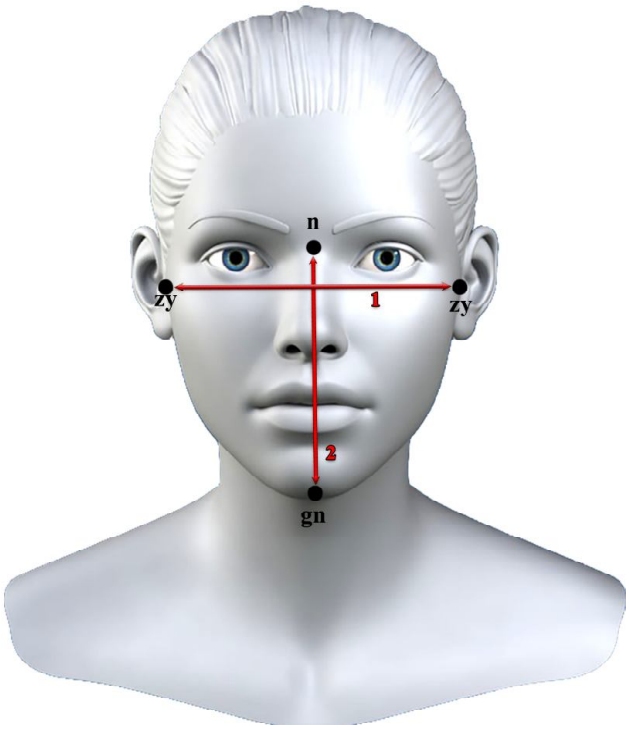

Fig. 1. Basic cephalometric points and measurements to determine the type of face according to the morphological index of Garson. **1 (zy_zy)** - the largest width of the face (distance between the cheekbones); **2 (n_gn)** - morphological length of the face (direct distance from the point nasion to the point gnathion).

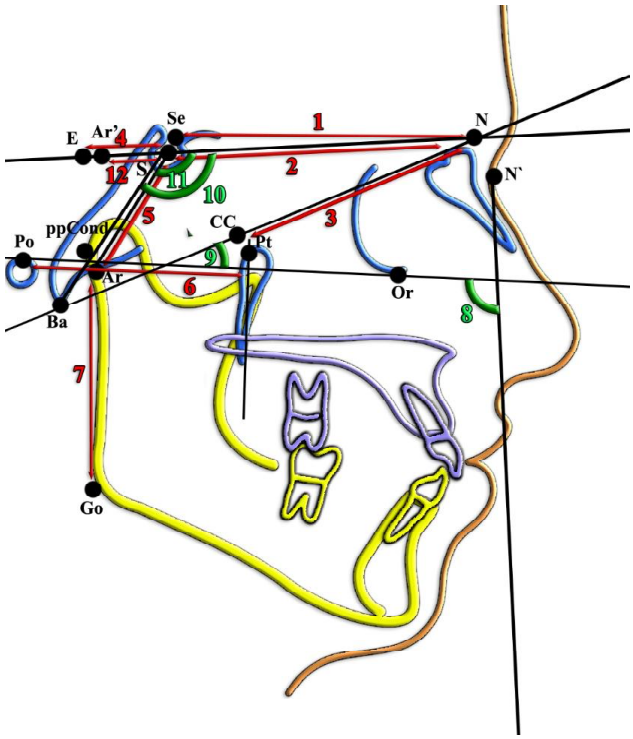

Fig. 2. Basic cephalometric points and measurements that usually do not change during surgical and orthodontic treatment. **1 (N-Se)** - (length of the front part of the skull base according to *Schwartz*, distance Se-N) - distance from the point **Se** to the point **N** (mm); **2 (N-S)** - (length of the front part of the base of the skull according to *Roth-Jarabak*) - the distance from point **N** to point **S** (mm); **3 (N-CC)** - (anterior length of the base of the skull according to *Ricketts*) - the distance from the point **N** to the point **CC** (mm); **4 (S-E)** - (length of the back of the skull base according to *Steiner*, distance S-E) - the distance from point **S** to the structural point **E**, which is located at the intersection of the perpendicular drawn from the point **ppCond** to the line **S-N** (mm); **5 (S-Ar)** - (length of the lateral cranial base according to *Roth-Jarabak*) - the distance from the point **S** to the point **Ar** (mm); **6 (P-PTV)** - (distance P-PTV according to *Ricketts*) - the distance from point **Po** to point **Pt**, determined parallel to the Frankfurt plane (mm); **7 (Ar-Go)** - (length of the branch of the lower jaw according to *Burstone*) - the distance from the point **Ar** to the point **tGo** (mm); **8 (H)** - (H-angle according to *Schwartz*) - the angle formed by the lines **Po-Or** (*Frankfurt plane **(Fp)***) and **Pn** (*nasal perpendicular, perpendicular to the line from the point **N'** to the line* **Se-N** (°); **9 (POr -NBa)** - (*Ricketts* cranial deflection angle) - angle formed by **Po-Or** and **Ba-N** lines (°); **10 (NS-Ba)** - (NS-Ba angle according to *Bjork*) - angle formed by **N-S** and **S-Ba** lines (°); **11 (NS-Ar)** - (saddle angle according to *Bjork*) - angle formed by lines **N-S** and **S-Ar** (°); **12 S-Ar'** - (distance of *Bjork* joint location) - distance from point **S** to point **Ar'**.

appropriate formula [19]: morphological length of the face / maximum width of the face x 100.

When the value of the indicator up to 78.9 young men or young women were attributed to group with a very wide face; 79.0-83.9 - with a wide face; 84.0-87.9 - with an average face; 88.0-92.9 - with a narrow face; 93.0 and more - with a very narrow face. The following distribution is established: young men with a very wide face - 5; young women with a very wide face - 25; young men with a wide face - 22; young women with a wide face - 25; young men with an average face - 11; young women with a medium face - 10; young men with a narrow face - 8; young women with a narrow face - 12.

The main cephalometric points and measurements are basic in modern cephalometric analyzes and are included in the parameters that usually do not change during surgical and orthodontic treatment are presented in Figure 2.

Estimated indicators are calculated on the basis of those shown in Figure 2: **N-S:S-Ar'** - the ratio of the distances **S-Ar' (12)** and **N-S (2)** in the cephalometric analysis of *Bjork*; **S-ar:ar-Go** - ratio of the distances **S-Ar (5)** and **Ar-Go (7)** in the *Roth-Jarabak* cephalometric analysis.

Statistical analysis of teleroentgenographic indicators was performed in the license package "Statistica 6.0" using non-parametric methods of evaluation of the obtained results.

Results

The percentage range of cephalometric parameters, which usually do not change during surgical and orthodontic treatment depending on the facial types of Ukrainian young men and young women with orthognathic occlusion are shown in Table 1.

When comparing the value of the distance **N-S** (according to Jarabak) in young men with very wide

Table 1. Percentage range (25.0th - 75.0th percentl) of cephalometric parameters, which usually do not change during surgical and orthodontic treatment depending on the facial types of Ukrainian young men and young women.

Indicator	Sex	Face type			
		very wide	wide	average	narrow
Angle N-S-Ar (°)	M	124.8 - 130.5	121.8 - 129.0	120.9 - 129.4	119.5 - 129.9
	W	120.2 - 129.6	121.4 - 128.4	123.9 - 129.5	120.9 - 129.2
Angle N-S-Ba (°)	M	129.6 - 132.9	126.6 - 132.5	124.7 - 133.8	123.2 - 132.3
	W	125.1 - 133.3	125.6 - 134.8	128.9 - 135.6	126.4 - 133.2
Ratio N-S:S-Ar'	M	3.2 - 3.6	3.1 - 4.1	3.3 - 4.2	3.0 - 4.05
	W	3.4 - 4.3	3.5 - 3.9	3.1 - 3.8	3.4 - 4.0
Distance N-S (mm)	M	70.0 - 13.5	12.8 - 13.5	12.8 - 13.5	12.8 - 13.5
	W	12.8 - 13.5	12.8 - 13.5	12.8 - 13.5	12.8 - 13.5
Distance N-S (mm)	M	31.0 - 36.0	33.0 - 37.0	33.0 - 38.0	35.0 - 37.5
	W	31.0 - 35.0	31.0 - 34.0	30.0 - 34.0	30.5 - 33.0
Ratio S-ar:ar-Go	M	54.0 - 69.0	59.0 - 73.0	60.0 - 72.0	64.5 - 71.0
	W	62.0 - 75.0	64.0 - 76.0	60.0 - 71.0	61.0 - 71.0
Distance Ar-Go (mm)	M	55.1 - 57.9	50.1 - 55.4	49.6 - 55.4	50.9 - 55.3
	W	44.3 - 49.4	44.0 - 49.1	43.3 - 50.7	45.7 - 49.0
Distance N-Se (mm)	M	69.0 - 70.0	67.0 - 70.0	68.0 - 71.0	67.0 - 72.5
	W	63.0 - 66.0	62.5 - 67.5	63.0 - 66.0	63.0 - 68.0
Angle H(°)	M	93.0 - 98.0	92.0 - 97.0	94.0 - 96.0	91.0 - 95.0
	W	92.0 - 96.0	93.0 - 95.0	93.0 - 98.0	92.0 - 96.5
Distance S-E (mm)	M	20.0 - 22.0	18.0 - 23.0	18.0 - 22.0	19.0 - 23.5
	W	16.0 - 20.0	18.0 - 21.0	18.0 - 22.0	16.5 - 19.0
Angle Por-NBa (°)	M	23.3 - 25.2	23.7 - 27.7	23.7 - 28.9	23.3 - 26.5
	W	23.4 - 26.2	25.3 - 27.5	24.7 - 28.1	24.4 - 26.8
Distance N-CC (mm)	M	56.5 - 59.7	56.6 - 59.8	55.5 - 58.9	57.7 - 60.3
	W	52.7 - 57.3	51.1 - 57.1	53.5 - 54.6	51.5 - 55.5
Distance P-PTV (mm)	M	-41.1 - -38.4	-42.3 - -38.2	-42.1 - -36.5	-41.7 - -38.9
	W	-38.9 - -34.9	-39.7 - -36.5	-39.7 - -34.9	-39.0 - -33.6

Notes: M - young men; W - young women.

(70.40±2.19 mm), wide (70.41±2.50 mm), medium (76.09±19.65 mm) and narrow (71.38±4.90 mm) face types are established reliably (p<0.05-0.01) higher values compared to young women of the corresponding type of face (respectively 67.92±6.99 mm - 67.32±5.06 mm - 66.10±2.33 mm - 66.08±3.34 mm).

The value of the **S-Ar** distance (according to Jarabak) in young men with wide (34.95±2.80 mm) and narrow (37.13±4.26 mm) face types is significantly (p<0.01-0.001) greater than in young women of the corresponding face type (respectively 32.72±3.14 mm - 31.50±2.02 mm).

When comparing the value of the distance **Ar-Go** (according to Burstone) in young men with very wide (56.38±2.80 mm), wide (52.67±5.13 mm), medium (56.11±16.53 mm) and narrow (53.59±3.37 mm) face types are established reliably (p<0.05-0.001) higher values compared to young women of the corresponding type of face (respectively 47.97±5.89 mm - 47.20±6.46 mm - 46.69±4.27 mm - 47.61±3.50 mm). Also, in young men with a very wide face, the value of this indicator tends (p=0.066) to higher values than in young men with a wide face.

The value of the distance **N-Se** (according to Schwarz) in young men with very wide (68.80±2.95 mm), wide (68.95±2.73 mm), medium (74.64 ± 19.46 mm) and narrow (70.50±4.96 mm) facial types significantly (p<0.05-0.001) is greater compared to young women of the corresponding type of face (respectively 66.28±6.78 mm - 65.42±5.37 mm - 64.70±2.31 mm - 65.50±3.29 mm).

When comparing the value of the distance **S-E** (according to Steiner) found only a tendency (p=0.054) to higher values of this indicator in young men with a narrow

(21.50±3.25 mm) face type compared to young women with a narrow face type (18.08±3.53).

When comparing the value of the angle **POr-NBa** (according to Ricketts) found only a tendency (p=0.074) to higher values of this indicator in young women with medium face type (26.76±1.95 mm) compared to young women with very wide face type (25.18±2.34 mm).

The value of the distance **N-CC** (according to Ricketts) in young men with very wide (58.56±2.24 mm), wide (57.59 ± 3.28 mm), medium (57.39±2.71 mm) and narrow (59.03±2.36 mm) facial types significantly (p<0.05-0.01) is greater compared to young women of the corresponding face type (respectively 56.22±6.22 mm - 54.45±3.72 mm - 54.37±2.86 mm - 53.76±3.05 mm).

When comparing the **P-PTV** distance (according to Ricketts) in young men with very wide (-40.18±2.48 mm), wide (-40.17±2.50 mm) and narrow (-40.01±3.85 mm) facial types, it was established reliably (p<0.05-0.01) higher values of this indicator compared to young women of the corresponding type of face (respectively -37.22±4.16 mm - -38.01±3.68 mm - -36.94±3.32 mm).

There are no significant or trend differences in the magnitude of the angles **N-S-Ar** (according to Bjork), **N-S-Ba** (according to Bjork) and H (according to Schwartz), as well as the ratios **N-S:S-Ar'** (according to Bjork) and **S-ar:ar-Go** (according to Jarabak) both between young men and young women of the corresponding face types, and between representatives of the corresponding sex of different face types.

Discussion

Thus, as a result of our research, pronounced manifestations of sexual dimorphism of only linear cephalometric parameters were established, which usually do not change during surgical and orthodontic treatment. Thus, young men with different face types have significantly greater values of N-S, Ar-Go, N-Se, N-CC, P-PTV and S-Ar distances than young women of the corresponding face types. For the magnitude of angles and ratios of cephalometric parameters, which usually do not change during surgical and orthodontic treatment, no manifestations of sexual dimorphism of these indicators were found between young men and young women of the corresponding face types. Also, we have not found significant or trends in the differences of these parameters between young men or between young women with different face types.

A group of authors led by Correa S. [4] found that most sizes of the branches of the mandible are the largest in brachycephalic (p<0.0001).

In a study conducted on ethnic Lebanese, it was found that men have higher upper and lower jaws parameters, while the ANB angle is higher in women. Lebanese women also have a more convex facial profile than men.

Teleroentgenograms of 46 men and 19 women aged 18-25 years, ethnic residents of Yemen, without orthodontic treatment in the anamnesis were studied and the data were statistically processed. It was found that Yemenis have higher SNA, SNB and SNPg angles [5].

The results of a study by Kolte R. A. and others [14] revealed that there are significant differences between the facial index, lip size and type of periodontium. For the most part, close correlations have been found between the thickness of the gums and the inclination of the front teeth of the mandible.

Laranjo F. and Pinho T. [15] studied the relationship between cephalometric and odontometric parameters in people with open bite. It was found that persons with an open bite have increased dental alveolar height of the upper and lower jaws and anterior height of the face.

Facial index scores were obtained for 33 people with a complete set of teeth and for 33 people with adentia. Also, each of the subjects underwent teleroentgenography to measure OP, FHP, CP, OP-FHP and OP-CP. After statistical processing, a positive correlation was found between TFI and OP-FHP, and a negative correlation for OP-FHP and OP-CP in individuals with a complete set of teeth [20].

44 young men of Ukrainian origin underwent a cephalometric, odontometric study with subsequent determination of the type of face in accordance with Garson's index. Statistical analysis of the data was used to develop regression models needed to construct correct dental arches. A total of 18 reliable models were built with a coefficient from 0.645 to 0.944 [16].

Summing up, it is safe to say that the study consistently complements and confirms the results of scientific work of other domestic and foreign researchers.

Conclusions

1. In Ukrainian young men and young women with orthognathic occlusion and different types of faces according to Garson, the percentile range of cephalometric parameters has been established, which usually do not change during surgical and orthodontic treatment.

2. The expressed manifestations of sexual dimorphism of cephalometric parameters which usually do not change during surgical and orthodontic treatment (bigger values at young men) are established only for the majority of the linear sizes at representatives of various types of face.

3. For cephalometric parameters, which usually do not change during surgical and orthodontic treatment in both young men and young women, there are almost no significant or tendencies of differences between representatives with different face types according to Garson.

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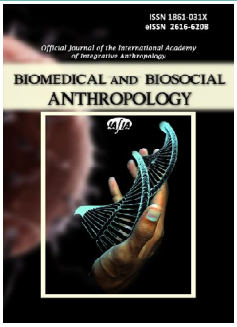

Evaluation of the effect of excess and deficiency of serum hydrogen sulfide on the condition of the vaginal wall of intact rats

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Various pathological conditions can be characterized not only by a decrease or increase in basal levels of hydrogen sulfide in the serum, but also the levels of hydrogen sulfide can modulate the course of the pathological process. The impact of serum hydrogen sulfide on the condition of the intact vaginal wall of rats was evaluated in this study. The aim of the study was to evaluate the effect of excess and deficiency of serum hydrogen sulfide on the condition of the vaginal wall of intact rats. The study was performed on 75 female Wistar rats under 1 year of age and weighing 160.0 to 200.0 grams. All animals were divided into 6 groups: control (intact rats); experimental 1 (H_2S excess); experimental 2 (H_2S deficiency); experimental 3 (intravaginal administration of suppositories with clindamycin); experimental 4 (H_2S excess + suppositories with clindamycin); experimental 5 (H_2S deficiency + suppositories with clindamycin). The levels of serum hydrogen sulfide were studied, as well as microscopic examination of the structure of the vaginal wall and determination of the levels of TNF-α and IL-1β in tissue homogenate were performed. In experimental groups 3, 4 and 5 all studies were performed in dynamics - 10 minutes, 4, 8 and 24 hours after a single intravaginal administration of clindamycin phosphate. The data were processed using the statistical software package SPSS 20.0 for Windows. Under conditions of both hydrogen sulfide deficiency and excess, no statistically significant changes in TNF-α and IL-1β levels in the vaginal wall of intact rats were observed. Also, no changes in the histological structure of the wall were found. Similar data were demonstrated in experimental groups 3, 4 and 5. This picture is explained by the fact that hydrogen sulfide affects various parts of the inflammatory process, while reducing the production of inflammatory mediators. In intact tissues, in the absence of an inflammatory process, there is no point of application of hydrogen sulfide, and therefore no significant changes are observed. Thus, both excess and deficiency of serum hydrogen sulfide do not affect the condition of the vaginal wall of intact rats.

Keywords: *hydrogen sulfide, vaginal wall, TNF-α, IL-1β, clindamycin phosphate, rats.*

Introduction

Despite the constant progress in clinical microbiology and pharmacology of antibacterial drugs, inflammatory diseases of the lower genital tract continue to occupy a leading place in the structure of obstetric and gynecological pathology. The most significant of these is bacterial vaginosis [1, 15].

This pathology is a serious health problem for women of reproductive age, their children and partners, as bacterial vaginosis is associated with adverse effects on reproductive health, such as pelvic inflammatory disease, miscarriage, premature birth, and can lead to increased risk of human immunodeficiency virus [7, 22, 23].

The social and practical significance of this pathology encourages the search for new mechanisms of control and modulation of the inflammatory process in the lower genital tract. One such modulator of the inflammatory process is hydrogen sulfide.

Since 1777, when the Swedish chemist Carl Wilhelm Scheele first synthesized hydrogen sulfide (H_2S), our ideas about this compound have undergone significant transformation. Hydrogen sulfide, which from the beginning was considered only as a highly toxic exogenous product of protein breakdown [13], is now recognized as one of the important endogenous factors in maintaining homeostasis.

Today, this compound belongs to the family of gas transmitters, which also includes nitrogen monoxide (NO) and carbon monoxide (CO). Hydrogen sulfide is involved in the regulation of vascular tone, neuromodulation, cytoprotection, inflammation, apoptosis and other processes [6, 18, 21].

For many years, various studies have indicated the role of hydrogen sulfide in the inflammatory process. Reactive forms of oxygen from activated neutrophils can oxidize H2S to form sulfite, which further enhances the regulation of leukocyte adhesion and neutrophil function by activating beta-integrin Mac-1 (CD11b/CD18) and Ca^{2+}/calmodulin dependent protein kinase, respectively [3, 4]. In addition, hydrogen sulfide has been shown to induce short-term granulocyte survival by inhibiting the cleavage of caspase-3 and mitogen-activated protein kinase p38 (MAPK) and thus contributing to the bactericidal activity of neutrophils [24].

It is proved that not only various pathological conditions can be characterized by a decrease or increase in the basal content of H_2S in blood plasma, but also the level of hydrogen sulfide itself can modulate the course of the pathological process [29].

At present, the scientific literature has virtually no information on the peculiarities of gynecological inflammatory diseases in conditions of excess and deficiency of serum hydrogen sulfide.

However, the study of the peculiarities of the inflammatory process in conditions of excess and deficiency of hydrogen sulfide, requires a preliminary study of the influence of similar factors on intact tissues.

That is why, in our opinion, it is important to study the condition of the intact wall of the vagina in conditions of excess and deficiency of serum hydrogen sulfide.

The aim of the study was to evaluate the effect of excess and deficiency of serum hydrogen sulfide on the condition of the vaginal wall of intact rats.

Materials and methods

The experimental study was performed on the basis of a research laboratory of preclinical study of pharmacological substances of National Pirogov Memorial Medical University, Vinnytsya.

All experiments were performed in accordance with the "Regulations on the use of animals in biomedical experiments" with the permission of the Bioethics Committee and in accordance with the provisions of Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 "On the protection of animals used for scientific purposes".

The study included 75 female Wistar rats under 1 year of age and weighing 160.0 to 200.0 grams (180.5±12.6 grams).

All rats were randomly divided into 6 groups:

control group (n=5) - intact animals;

experimental group 1 (n=5) - rats with excess hydrogen sulfide;

experimental group 2 (n=5) - rats with hydrogen sulfide deficiency;

experimental group 3 (n=20) - rats, which were intravaginally administered clindamycin phosphate in the form of suppositories;

experimental group 4 (n=20) - rats with excess hydrogen sulfide, which were intravaginally administered clindamycin phosphate in the form of suppositories;

experimental group 5 (n=20) - rats with hydrogen sulfide deficiency, which were intravaginally administered clindamycin phosphate in the form of suppositories.

Groups with intravaginal administration of clindamycin phosphate in the form of suppositories were included in the study, as this antibiotic is the drug of choice and an integral part of the comprehensive treatment of inflammatory diseases of the vagina [14, 27]. Although clindamycin phosphate does not have a local irritant or anti-inflammatory effect [19], its effect on the vaginal wall in conditions of excess or deficiency of hydrogen sulfide requires careful study.

To synchronize estrous cycles, all test animals were injected subcutaneously with 17α-hydroxy-6α-methylprogesterone (Pfizer Inc., USA), diluted in Ringer's solution lactate at a dose of 12 mg per test animal 7 and 3 days before the study date [5].

The dose of 12 mg per experimental rat was determined by recalculating the dose of the drug for mice. The dose was recalculated according to the method proposed by Nair A. B. and Jacob S. [20].

The synchronization of estrous cycles was checked immediately before the start of a set of manipulations to study the condition of the vaginal wall, by microscopy of smears from the vagina of experimental animals according to the criteria described by Fu X. Y. and co-authors [9].

Excess hydrogen sulfide in animals was created by intraperitoneal administration of donor H_2S - sodium hydrosulfide (Sigma-Aldrich, USA) at a dose of 1.5 mg/kg on 0.1 M phosphate buffer (pH 7.4), as a freshly prepared aqueous solution at the rate of 0.1 ml per 100 g weight rat, once a day for 5 days immediately preceding the date of the study of the vaginal wall [28].

Hydrogen sulfide deficiency was created by the introduction of a specific inhibitor of cystathionine gamma-lyase - D, L-propargylglycine (Sigma-Aldrich, USA) at a dose of 50 mg/kg as a freshly prepared 5 % aqueous solution at the rate of 0.1 ml per 100 g of rat weight once a day for 5 days immediately preceding the date of the study of the condition of the vaginal wall [28].

Clindamycin phosphate (Pfizer Inc., USA) was administered to rats intravaginally as micro-suppositories. The dose of the drug according to the conversion tables was 1.5 mg [20]. Given that the suppository contains 100 mg of active substance and weighs 2.5 grams, and based on the fact that the active substance is evenly distributed in the suppository, to provide an equivalent dose (1.5 mg of

In each group and at each time point, the condition of the vaginal wall was studied in 5 rats.

To assess the condition of the vaginal wall, a

microscopic examination of its structure was performed and the levels of TNF-α and IL-1β in the tissue homogenate were determined.

The study of the condition of the vaginal wall in experimental groups 2, 4 and 6 was performed in the dynamics - 10 minutes, 4, 8 and 24 hours after a single intravaginal administration of clindamycin phosphate, according to the method of cervical toxicity and inflammation of local intravaginal dosage forms described by Catalone B. J. and co-authors [5] and adapted by us for research on laboratory rats.

Blood sampling to determine the level of hydrogen sulfide was performed by percutaneous puncture of the heart under ketamine anesthesia at the rate of 0.22 ml of ketamine per 100 grams of body weight of the experimental animal. The content of hydrogen sulfide in blood serum was determined by spectrophotometric method in the reaction between sulfide anion and para-phenylenediamine hydrochloride in an acidic environment in the presence of iron ions (III) [28].

After blood collection, rats were removed from the experiment by translocation of the cervical vertebrae.

The vagina was removed and washed from the remnants of blood in saline, followed by careful drying of the tissues with a sterile napkin. The removed organ was cut in the longitudinal direction into 4 equal parts. Three parts were fixed in 10% neutral formalin solution and sent for microscopic examination. The latter fragment was homogenized by adding 1 ml of phosphate buffer in an automatic tissue disaggregator Medimax (CTSV, Italy) using disposable Medicon cartridges (Becton Dickinson, USA) with pyramidal blades of 35 μm. The tissue homogenate was then filtered through Filcon filters (Becton Dickinson, USA) with a pore diameter of 30 μm.

The levels of TNF-α and IL-1β in the vaginal tissue homogenate filtrate were investigated by enzyme-linked immunosorbent assay using the Rat TNF-α ELISA kit and Rat IL-1β ELISA Kit (CUSABIO, China).

After fixing the preparation of the vagina in a 10 % solution of neutral formalin for 3 days, the preparations were prepared according to standard methods. Paraffin sections 5-7 μm thick were stained with hematoxylin and eosin. Microscopy and photographing of histological specimens were performed using a light microscope OLIMPUS BX 41 at magnifications of 40, 100, 200, 400 and 1000. Microscopy assessed the condition of all layers of the body. Images were obtained and processed, and morphometry was performed using the program "Quick PHOTO MICRO 2.3".

The obtained data were processed using the statistical software package SPSS 20.0 for Windows.

Results

In all groups and at all times of the study, no behavioral changes were observed in experimental animals. All rats maintained normal motor activity. Consumption of feed and water met the standards for this species.

Evaluation of the synchronization of estrous cycles showed the presence of the same changes in the microscopic examination of vaginal swabs. The smears showed a small number of cells, with a predominance of small epitheliocytes with nuclei and almost complete absence of neutrophils, large epitheliocytes with nuclei and non-nuclear keratinized epitheliocytes. According to the criteria described by Fu X. Y. and co-authors [9], this picture was identified by us as characteristic of proestrus.

Serum hydrogen sulfide levels in groups of experimental animals are shown in Figure 1.

The level of serum hydrogen sulfide in the control group was 75.60±5.05 μmol/L. In experimental group 1, where an excess of hydrogen sulfide was artificially created, this indicator significantly ($p<0.01$) increased by 16.3 % compared with the control group. In experimental group 3 (hydrogen sulfide deficiency) there was a significant ($p<0.01$) decrease in serum H_2S by 22.4 %.

The serum hydrogen sulfide values in animals of experimental groups 3, 4 and 5 did not differ significantly ($p>0.05$) from similar indicators in the control group and experimental groups 1 and 2, respectively.

Macroscopic evaluation of vaginal preparations revealed no changes. The mucosa of the organ in all samples had a normal color, hemorrhage, visible damage, ulcers or punctate erosions were not observed.

Microscopic examination of the vaginal wall in rats of all groups showed a typical pattern characteristic of the proestrus phase (Fig. 2). The integrity of the vaginal wall is not violated. The mucous membrane is represented by a multilayered epithelium with cuboid and ovoid cells. Epithelial degeneration and desquamation are virtually absent. Single keratinized epitheliocytes are observed.

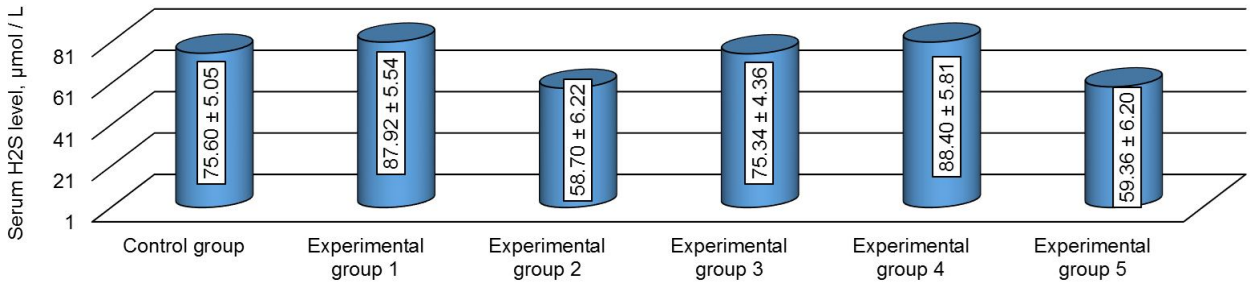

Fig. 1. Serum hydrogen sulfide levels in groups of experimental animals.

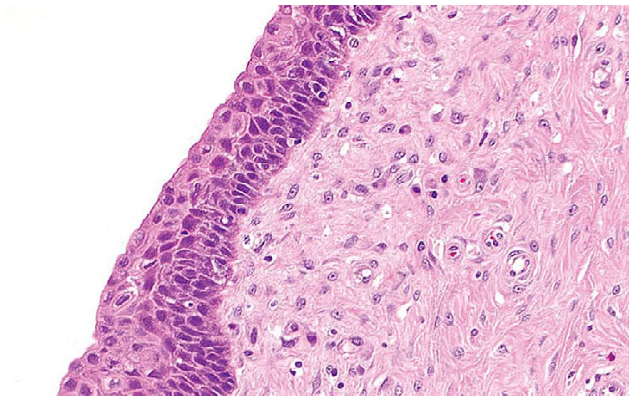

Fig. 2. Typical morphological picture of the vaginal wall of experimental rats in the proestrus phase.

Table 1. TNF-α and IL-1β levels in the vaginal wall of intact rats, as well as in conditions of excess and deficiency of hydrogen sulfide.

Group	TNF-α, pg/mL	IL-1β, pg/mL
Control	45.25±5.68	218.5±20.3
Experimental group 1	44.94±5.16	215.4±21.6
Experimental group 2	47.12±5.75	223.6±18.0

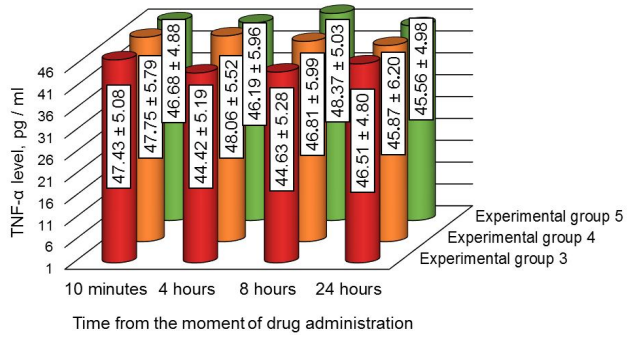

Fig. 3. Dynamics of changes in TNF-α levels in the vaginal wall.

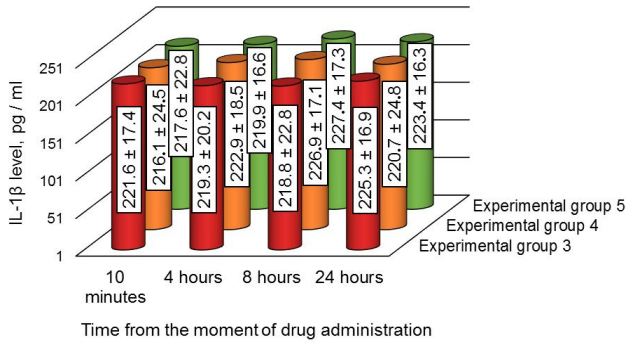

Fig. 4. Dynamics of changes in IL-1β levels in the vaginal wall.

Mitotic figures are observed. Polymorphic structures are present in some places.

As can be seen from Table 1, the numerical values of both TNF-α and IL-1β are slightly reduced under conditions of excess hydrogen sulfide in the body of experimental rats and increase under conditions of its deficiency. However, it should be noted that these level fluctuations did not exceed 4 % relative to those in intact rats and did not differ significantly from them, as well as from each other in the statistical analysis ($p>0.05$).

The data obtained by analyzing the dynamics of changes in the levels of TNF-α and IL-1β in the vaginal wall using the intravaginal form of clindamycin phosphate are graphically depicted in the diagrams (Fig. 3, 4).

As can be seen from Figures 3 and 4, in all groups there were slight fluctuations in the studied indicators. However, it should be noted that no significant statistical differences between the indicators of different groups at each time point were demonstrated ($p>0.05$). In addition, there was no clear tendency to change over time in each of the groups ($p>0.05$).

Discussion

At present, one of the most probable and well-founded mechanisms of protective effect of hydrogen sulfide in the inflammatory process is the blockade of the signaling pathway of mitogen-activated protein kinase p38 (MAPK) [25, 30]. Regulation of MAPK activity mediates inflammation and/or oxidation, thus exacerbating tissue damage. Hydrogen sulfide, by inhibiting the activation of the MAPK signaling pathway, indirectly protects tissues from inflammation. The expression of MAPK and ERK 1/2 (kinases regulated by extracellular signals) was reduced with the use of hydrogen sulfide in a model of inflammation and hypoxic damage in cell cultures [16].

In addition to protein kinases, nuclear factor kappa-B (NF-κB) and nuclear factor 2 associated with erythroid 2 (Nrf2) play an active role in the development of the inflammatory process [2]. NF-κB is responsible for the transcription of many genes involved in inflammation and is activated in many acute and chronic inflammatory diseases, such as sepsis, inflammatory bowel disease, arthritis, asthma. Nrf2 belongs to a family of proteins that regulate endogenous antioxidant protection and promotes the transcription of a set of detoxifying genes that encode proteins (such as enzymes, drug transporters, antiapoptotic proteins, and proteasomes) involved in the regulation of physiological and pathophysiological cellular responses to oxidants and xenobiotics.

F. Benedetti and co-authors [2] demonstrated that hydrogen sulfide not only inhibits NF-κB activation and nuclear translocation by reducing the transcription of proinflammatory genes, but also enhances Nrf2 function by activating a cascade of enzymes such as hemoxygenase-1 (HO-1) superoxide dismutase-1 (SOD1).

The main substrates for endogenous hydrogen sulfide in tissues are sulfur-containing amino acids - L-cysteine and L-homocysteine, its main enzymes-producers are pyridoxal phosphate-dependent enzymes cystathionine-β-synthase, cystathionine-γ-lyase, as well as cysteine aminotransferase [26].

The main reactions that ensure the formation of hydrogen sulfide in animal and human tissues include

[26]: desulfurization of L-cysteine to pyruvate with cystathionine-γ-lyase; condensation of L-homocysteine with L-cysteine and desulfurization of L-cysteine to L-serine with the participation of cystathionine-β-synthase; transamination of L-cysteine with α-ketoglutarate with the participation of cysteine aminotransferase with the formation of 3-mercaptopyruvate, from which further H2S is released with the participation of 3-mercaptopyruvate sulfurtransferase.

The introduction of sodium hydrosulfide as a donor of hydrogen sulfide and propargylglycine as a selective inhibitor of cystathionine-γ-lyase synthesis (key enzyme-producer of H_2S) allows to significantly change the levels of serum hydrogen sulfide and modulate a wide range of physiological, and pathophysiological processes [6, 12, 18, 21].

The methods used in our study [28] allowed to create a statistically significant excess and deficiency of hydrogen sulfide in experimental rats. In conditions of both deficiency and excess of hydrogen sulfide, statistically significant changes in the levels of TNF-α and IL-1βin the vaginal wall of intact rats could not be achieved. Regardless of the level of serum hydrogen sulfide, we did not observe any changes in the histological structure of the vaginal wall.

This picture is explained by the fact that hydrogen sulfide affects various parts of the inflammatory process, while reducing the production of inflammatory mediators. In intact tissues, in the absence of an inflammatory process, there is no point of application of hydrogen sulfide, and therefore no significant changes are observed.

The absence of pro- and/or anti-inflammatory effect in the modulation of serum hydrogen sulfide levels in rats without signs of inflammation has been repeatedly described in the scientific literature. Thus, other authors have demonstrated the absence of morphological changes and changes in the levels of inflammatory mediators (TNF-α and/or IL-1β) in the study of the hippocampus, kidneys, heart, lungs [10, 11, 17, 25, 30].

In addition, both in conditions of deficiency and in conditions of excess hydrogen sulfide, no statistically significant differences in the levels of the studied mediators of inflammation were demonstrated with topical application of clindamycin phosphate in the form of suppositories. The absence of changes in the vaginal wall in these groups of experimental rats was also not demonstrated in the morphological study.

The lack of dynamics of markers of inflammation and morphological changes of the vaginal wall, in our opinion, can be explained by the gentle effect of clindamycin phosphate on the vaginal mucosa and the lack of local irritant effect [8, 19].

The effect of excess and deficiency of hydrogen sulfide on the condition of the vaginal wall in the local inflammatory process requires further careful research.

Conclusions

1. Both excess and deficiency of hydrogen sulfide do not affect the condition of the vaginal wall in intact rats, as evidenced by the absence of changes in local levels of TNF-α and IL-1β, as well as microscopic changes in morphological examination.

2. Regardless of the background level of hydrogen sulfide, clindamycin phosphate when administered intravaginally in the form of suppositories does not affect the condition of the vaginal wall of intact rats.

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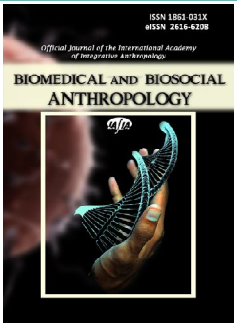

Actual aspects of traumatic pathology among servicemen of Ukrainian Armed Forces in Joint Forces Operation

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The use of these traditional peacetime methodological approaches to accounting and analysis of non-combat injuries has led to an underestimation of its high level in the planning of inpatient care for servicemen of the Armed Forces of Ukraine in the area of the Joint Forces operation (anti-terrorist operation). The purpose of the study is a general assessment of the place of combat and non-combat injuries (including poisoning) in the structure of cases of hospitalization of servicemen of the Armed Forces of Ukraine in the area of the Joint Forces operation and anti-terrorist operation. Statistical mathematical processing was performed using computer programs Microsoft Excel and STATISTICA (version 6, StatSoft, Inc.). Based on annual medical reports on 3/med form, the ICD-10 structure of Ukrainian Armed Forces servicemen treated in MTF located in area of Joint Forces Operation for 2015-2020 has been presented. Ranks of disease classes have been calculated. Based on medical reports according Temporary instruction on codification of battle injures, non-battle trauma and diseases in Ukrainian Armed Forces, the structure of casualties admissions to MTF have been pointed out. The leading places in structure of treated servicemen belongs to patients with diagnoses on XIX class of ICD-10 (1st place for 2015-2019, 2nd place in 2020) that was stipulated by relative high levels of non-battle trauma in troops on the East of Ukraine. The comparison of structure of servicemen treated in MTF located in and out area of Joint Forces Operation as well as with structure of adult population (over 18 years old) treated in civil hospitals has been conducted. Prevalence of traumatic pathology levels among patients treated in MTF located in area of Joint Forces Operation in comparison with others treatment facilities data has been revealed. For 2015-2020 the shares of trauma and poison cases in structure of treated servicemen in MTF located in area of Joint Forces Operation significantly decreased that was connected with gradual lowing of battle actions intensity and non-battle trauma level. Based on result of research the necessity to improve curative and diagnostic base of military treatment facilities in area of Joint task operation as well as medical report and non-battle trauma prevention systems has been concluded.

Keywords: *non-battle trauma, structure of treated patients, servicemen of the Armed Forces of Ukraine (anti-terrorist operation), Joint Forces Operation, military mobile hospitals.*

Introduction

The share of traumatic pathology in the structure of treated patients is an important indicator that determines the activities of health care facilities of the Armed Forces of Ukraine due to the fact that treatment of injuries is high, requires modern medical and diagnostic equipment and significant costs of material, technical and human resources [3].

The system of collecting medical static data and methodological approaches used for their analysis in the medical service of the Armed Forces of Ukraine do not allow to fully assess the impact of injuries among servicemen of the Armed Forces of Ukraine on the work of military medical facilities in the area of JFO (anti-terrorist operation). In particular, the statistical observations focused primarily on the structure of injuries, namely, mainly studied their structure by location, as well as the causes and

circumstances of injuries [3, 4, 19].

As a result of using these traditional methodological approaches in peacetime to the accounting and analysis of non-combat injuries led to an underestimation of its high level during the planning of inpatient care for servicemen of the Armed Forces of Ukraine in the area of the Joint Forces operation (anti-terrorist operation) which determined the relevance of this study.

The purpose of the study is a general assessment of the place of combat and non-combat injuries (including poisoning) in the structure of cases of hospitalization of servicemen of the Armed Forces of Ukraine in the area of the Joint Forces operation and anti-terrorist operation.

Materials and methods

The source of data on the magnitude, circumstances and causes of injuries of servicemen of the Armed Forces of Ukraine in the area of the Joint Forces operation (anti-terrorist operation) (hereinafter - JFO and ATO, respectively) were reports provided by health facilities of the Armed Forces of Ukraine under the Interim Instruction codification of combat injuries, non-combat injuries and diseases in the Armed Forces of Ukraine, approved by the order of the Director of the Military Medical Department of the Ministry of Defense of Ukraine dated 28.12.2016 № 37 (hereinafter - the Temporary Codification Instruction).

The source of data on the structure of treated patients in mobile military hospitals were medical reports in the form of 3/Med, which until 2017 were provided in the form of certain reports, and from 2017 - according to the orders of the governing body implementing the state policy in the Armed Forces in the field of health care of servicemen, members of their families and other categories of citizens defined by the legislation of Ukraine (currently it is the Command of the Medical Forces of the Armed Forces of Ukraine, hereinafter - the CMF) [5].

Statistical analysis of available research materials was performed using standard methods of mathematical statistics. Statistical mathematical processing was performed using computer programs Microsoft Excel from Microsoft Office and STATISTICA (version 6, StatSoft, Inc.).

Results

Despite a certain decrease in the number of cases of hospitalization of servicemen due to non-combat injuries in the area of JFO/anti-terrorist operation during 2015-2020, its level remains relatively high, especially considering that in most cases injuries of servicemen are related to human factors. can potentially be prevented through preventive measures. We found that the ratio of combat injuries to non-combat injuries among servicemen - members of the ATO (JFO) in 2017 was - 1: 1.19; 2018 - 1: 1.36; 2019 - 1: 1.33; 2020 - 1: 1.57, which indicates the need to pay more attention to the prevention of non-combat injuries in the inter-combat period.

Next, we analyze the place of injuries in the general structure of hospitalizations in health care facilities of the Armed Forces of Ukraine in the area of JFO (ATO), which gives grounds to emphasize the need to improve the existing system of medical accounting and reporting, as well as the need to improve logistics Forces of Ukraine.

Our calculated structure of servicemen of the Armed Forces of Ukraine, treated during 2015-2020 in military hospitals stationed in the area of the Joint Forces operation (anti-terrorist operation), indicates that during 2015-2019 the first place in the structure of treated military patients diagnosed with class XIX ICD-10 "Injuries, poisoning and some other consequences of external causes" (35.39 %, 27.39 %, 26.44 %, 22.55 % and 17.12 % respectively), the second - class X diseases "Respiratory diseases" (13.54 %, 20.14 %, 16.64 %, 16.98 % and 16.96 % respectively). Only in 2020, class X diseases in the structure took the traditional 1st place (18.21 %), pushed to 2nd place class XIX (16.06 %). In this case, according to Fisher's - transformation criterion (see [1]), the proportion of patients in class XIX differed significantly from the proportion of patients in class X ($p<0.001$).

Regarding other classes of diseases, in different years 3, 4 and 5 rank place in different combinations in the structure of treated servicemen was occupied by diseases of XI class "Digestive diseases", XIII class "Diseases of the musculoskeletal system and connective tissue" and IX class "Diseases of the circulatory system."

At first glance, it is thought that injuries and poisonings occupy such an important place in the structure of treated patients as a result of admission to hospitals stationed in the area of JFO (ATO) wounded during hostilities related to combat casualties. But according to reports provided under the Provisional Instruction on Codification, the XIX class took first place in the structure largely due to cases of hospitalization of servicemen who received non-combat injuries.

It should be noted that the share of servicemen of the Armed Forces of Ukraine hospitalized for non-combat injuries decreased more than 2 times: from 17.36 % in 2017 to 7.99 % in 2020 (Table 1).

If we compare the obtained statistics with the structure of classes ICD-10 servicemen treated in other health care facilities of the Armed Forces of Ukraine, and the structure of adult patients (aged 18 and older) who left the hospitals of health care facilities of Ukraine [11-16], you can see the following (Table 2):

the share of servicemen treated in military hospitals stationed outside the area of JFO (ATO), whose diagnoses belong to the XIX class of diseases, took in 2015 2nd place, in 2016 - 4th place, in 2017-2020 - 5th rank (in the general structure for all classes of diseases);

the share of patients treated in civilian health care facilities of Ukraine, whose diagnoses belong to the XIX class of diseases, took a stable 7th place during 2015-2020.

The estimation of the tendency of change of the share

Table 1. The structure of the inflow of patients to military hospitals in the area of the Joint Forces operation (anti-terrorist operation) in eastern Ukraine by categories of sanitary losses for the period 2017-2020, %.

Health institution	Combat defeat (injury, wounding)				Non-combat trauma *				Disease			
	2017	2018	2019	2020	2017	2018	2019	2020	2017	2018	2019	2020
59 MMH	**	9.28	5.62	6.35	**	12.12	7.64	8.17	**	78.60	86.74	85.48
66 MMH	16.54	9.18	6.63	6.14	15.55	12.72	11.53	8.45	67.91	78.10	81.85	85.40
65 MMH	16.25	7.11	7.54	3.88	23.12	9.75	6.72	7.72	60.63	83.13	85.75	88.40
61 MMH	8.46	10.08	8.08	5.42	11.39	13.20	11.58	8.86	80.15	76.72	80.34	85.71
450 MH	6.36	0.40	-	-	4.65	3.95	-	-	89.00	95.65	-	-
385 MH	25.00	0	11.54	0	25.00	0	50.00	0	50.00	100	38.46	100
Military Medical Clinical Center of the Northern Region (Kharkiv)	6.01	0	3.53	2.38	1.91	0	0.59	1.02	92.08	100	95.88	96.60
555 MH	-	-	-	1.07	-	-	-	9.01	-	-	-	89.91
All institutions	14.63	8.39	6.87	5.09	17.36	11.38	9.13	7.99	68.01	80.24	84.00	86.92

Notes: * - the following groups of diagnoses of the XIX class were carried to diseases: poisoning by medicines and biological substances. (T36-T50); toxic effects of substances, mainly non-medical purposes (T51-T65); other and unspecified effects of external causes (T66-T78); complications of surgical and therapeutic interventions, which are not classified in other headings (T80-T88); consequences of injuries, poisonings and other influences of external causes (T90-T98); ** - in the report 59 MMH for 2017 cases of hospitalization for diseases were not presented.

Table 2. The structure of patients in certain classes of ICD-10, discharged from hospitals of health care institutions for the period 2015-2020, %.

Classes of diseases	Codes according to ICD-10	The structure of patients of all categories who left the civilian health care facilities of Ukraine						Structure of servicemen who left military hospitals (excluding JFO facilities)					
		2015	2016	2017	2018	2019	2020	2015	2016	2017	2018	2019	2020
Class V. Mental and behavioral disorders	F00-F99	4.29	4.31	4.34	4.55	4.54	4.83	5.43	4.29	4.85	5.33	4.85	3.96
Class IX. Diseases of the circulatory system	I00-I99	22.12	22.05	22.75	22.80	23.19	19.94	10.74	10.65	12.13	13.09	13.87	15.42
Class X. Diseases of the respiratory system	J00-J99	8.35	9.29	8.14	8.23	8.04	11.89	22.48	26.41	23.16	22.40	22.39	24.51
Class XI. Diseases of the digestive system	K00-K93	9.35	9.09	9.29	9.22	9.07	8.71	9.56	10.01	10.27	9.98	10.03	8.97
Class XIII. Diseases of the musculoskeletal system	M00-M99	6.35	6.21	6.32	6.45	6.53	4.87	10.47	10.08	11.67	11.75	11.71	10.03
Class XIX. Injuries and poisoning	S00-T98	7.10	7.10	7.12	6.94	6.81	6.73	16.48	10.03	8.73	7.46	7.04	7.06

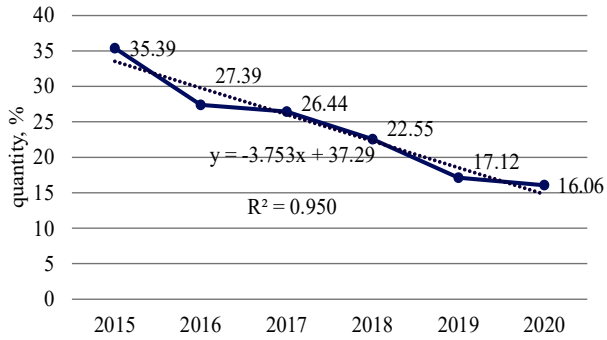

Fig. 1. Assessment of the trend of changes in the proportion of patients hospitalized in health care facilities of the Armed Forces of Ukraine in the area of JFO/ATO for pathological conditions belonging to the XIX class of diseases according to ICD-10.

of patients hospitalized to the health care institutions of the Armed Forces of Ukraine in the area of JFO (ATO) concerning pathological conditions belonging to the XIX class of diseases according to ICD-10 is given in Fig. 1.

As can be seen from Fig. 1, the share of patients with pathology classified as class XIX diseases decreased annually by an average of 15.12 %, which can be explained by the implementation of a set of measures to implement the Minsk agreements in eastern Ukraine, as well as the introduction of a ceasefire on July 27, 2020.

This was due to a correlated decrease in the proportion of servicemen hospitalized with combat injuries (wounds, injuries) and servicemen hospitalized for non-combat injuries (correlation coefficient R=0.997, p<0.001).

Discussion

The system of injury prevention in the Armed Forces of Ukraine needs further improvement, in particular, in our opinion, the system of medical accounting and reporting of casualties of the Armed Forces of Ukraine needs to be revised.

Thus, in the classifications of types of losses of personnel of the Armed Forces of Ukraine, given in the Instruction on medical support of the Armed Forces of Ukraine for a special period [9], approved by the order of the General Staff of the Armed Forces of Ukraine from 11.02.2019 № 60, and Methodical manual personnel of the Armed Forces of Ukraine [8], approved by the Chief of the General Staff - Commander-in-Chief of the Armed Forces of Ukraine on October 29, 2019, non-combat injuries are not allocated to a separate accounting category.

At the same time, the NATO Doctrine of Health Care ("AJP-4.10 Ed. C Ver. 1 Allied joint doctrine for medical support") [17] and the NATO Doctrine of Health Care Planning ("AJMedP-1 Ed. A Ver. 1 Allied joint medical planning doctrine") [18] non-combat injuries are a separate category of sanitary losses, which is taken into account when planning the medical support of troops (forces). In particular, when planning medical care, the calculation of projected losses by patients and injured is carried out according to separate coefficients.

Imperfect and insufficient for the analysis of causal relationships is the classification of causes and circumstances of injuries, which is used in filling out the annual medical reports of military medical institutions on the form 2/Med [10]. In this regard, it is advisable to develop and implement a classification similar to the NATO standard "Statistical Classification of Diseases, Injuries and Causes of Death" (STANAG 2050 "Statistical Classification of Diseases, Injuries and Causes of Death"), which provides greater opportunities for injury analysis for the reasons of its occurrence.

The report of the Working Group on Injury Prevention of the US Armed Forces Epidemiological Administration [2] stressed the importance of introducing a trauma monitoring system and its use as a basis for developing targeted measures to prevent injuries in the military. The importance of using different standardized injury classifiers (by type of injury, by the striking cause of the injury, by the location of the injury) is emphasized, which reflects the multidimensional classification approach. At the same time, in order to avoid accounting errors due to the human factor, these classifiers should have a minimized content sufficient to analyze the phenomenon of injuries in military teams. Thus, according to the analysis of medical accounting systems, foreign researchers state that in a fairly large proportion of cases of codification of injuries, the requirements of STANAG 2050 were ignored. This may have been due to the excessive scope of this classification and the ambiguity in the interpretation of individual classification headings. Therefore, the use of approaches (implementation) of STANAG 2050 should be carried out carefully (with national notes and deviations), taking into account the existing system of medical accounting and reporting in the Armed Forces of Ukraine.

The classification of circumstances and causes of injuries, which was used in domestic accounting documents of the medical service had its evolutionary development. It was based on the principle of distribution of losses according to the circumstances and causes of their occurrence, ie indicated the general type of activity in which the injury occurred, and the reasons for their occurrence.

Their analysis shows that domestic classifications of injuries were presented in the form of two-dimensional matrices of circumstances and causes of injuries and characterized injuries only from a general standpoint, without emphasizing the variety of striking effects on which prevention work should focus on injury prevention.

It should be noted that currently the analysis of injuries in the medical service of the Armed Forces of Ukraine is conducted only once a year on the basis of generalization and processing of reports of medical reports of military units (military authorities) on form 2/Med.

That is, the improvement of the system of medical accounting and reporting in terms of injury monitoring should include: the importance of processing reporting documents; the possibility of developing proposals for the prevention of injuries in the military, based on new principles of classification of injuries; feedback with accountables in order to ensure the correctness and completeness of accounting, control over the implementation of measures to prevent injuries, as well as possible hereditary correction of classification approaches.

Based on the statistical material analyzed by us, the prevalence of pathological conditions belonging to the XIX class of diseases according to ICD-10 in the structure of hospitalizations to health care facilities of the Armed Forces of Ukraine in the area of JFO (ATO) is convincingly shown.

The predominance of traumatic pathology in the structure of patients treated in military hospitals stationed in the area of JFO (ATO) necessitates the improvement of medical and diagnostic equipment of these institutions.

To this end, the norms of supply of medical equipment of military mobile hospitals [7] introduced a mobile surgical room based on the KRAZ car and a mobile X-ray diagnostic complex based on a car with a digital X-ray machine (mobile X-ray room on the basis of the KRAZ car) which are admitted to operation in Armed Forces of Ukraine by order of the Ministry of Defense of Ukraine dated 27.03.2017 № 179 [6].

In addition, in our opinion, it is advisable to strengthen the diagnostic capabilities of military mobile hospitals through mobile computed tomography systems and mobile surgical modules, for example, on 2 operating tables, etc.

In general, based on the above study, it can be stated that the provision of medical care to patients with injuries

and poisonings was and remains one of the highest priorities of the medical service of the Armed Forces of Ukraine in the area of JFO (ATO), even under ceasefire.

Conclusions

1. According to the results of the study, it was established that in the structure of servicemen of the Armed Forces of Ukraine treated in health care facilities of the Armed Forces of Ukraine stationed in the area of JFO (ATO), the leading place (1st place in 2015-2019 and 2 place in 2020) is the share of patients with diagnoses belonging to the XIX class of ICD-10 "Injuries, poisoning and some other consequences of external causes" (35.39 % in 2015, 27.39 % in 2016, 26.44 % in 2017, 22.55 % in 2018, 17.12 % in 2019 and 16.06 % in 2020), which is significantly larger than the share of similar patients in other health care facilities of the Armed Forces of Ukraine as a whole.

2. The predominance in the structure of servicemen of the Armed Forces of Ukraine treated in health care facilities of the Armed Forces of Ukraine in the area of JFO (ATO), the share of patients diagnosed with class XIX diseases ICD-10 in particular due to high non-combat injuries (non-combat injuries share in the structure of hospitalized amounted to 17.36 % in 2017, 11.38 % in 2018, 9.13 % in 2019 and 7.99 % in 2020).

3. Determining the features of the structure of servicemen treated in health care facilities of the Armed Forces of Ukraine in the area of JFO (ATO), necessitate improvement of the system of medical accounting and reporting in the Armed Forces of Ukraine, in particular taking into account the experience of medical accounting and reporting in the NATO Armed Forces, as well as a basis for clarifying the profiling of the bed stock, amendments to supply standards, staffs and tables to the staffs of health facilities (including military mobile hospitals) concerning the quantitative and qualitative improvement of medical equipment and property intended for the treatment of patients with surgical and traumatological profile.

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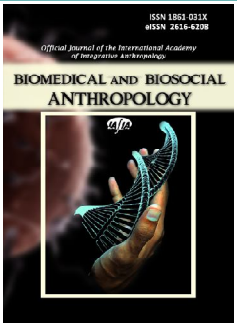

Investigation of 4-methyl-2.2-dioxo-1h-2λ^6,1-benzothiazine-3-carboxamide derivative influence on the biochemical markers of gastric mucosa in rats

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Non-steroidal anti-inflammatory drugs occupy a leading position in the pharmaceutical market, but their class-specific side effect (ulcerogenic action) significantly limits their widespread use. The N-(4-methoxybenzyl)-4-methyl-2,2-dioxo-1H-2λ^6,1-benzothiazine-3-carboxamide derivative (compound NI-9) showed a pronounced analgesic effect in various models of pain syndromes. The aim of the study was to determine the effect of a new original derivative of 4-methyl-2.2-dixo-1H-2λ^6,1-benzothiazine-3-carboxylic acid on the macroscopic state and biochemical parameters of the gastric mucosa of rats. The study was performed on 51 male Wistar rats. Compound NI-9 and the reference drug meloxicam were administered intragastrically once daily for 28 days at doses of 3 and 5 mg/kg, corresponding to their ED50 analgesic activity. Macroscopic indicators of GM damage, glycosaminoglycan content, phospholipid profile, level of MDA and CGP, as well as nitrates and nitrites and H_2S were determined. The results were processed in the program STATISTICA 10.0 using non-parametric methods. The results showed that the carboxamide derivative was safer for the stomach because the ulcer index of compound NI-9 was 1.73 times lower than that of meloxicam. The damaging effect of the compound was more pronounced at the pre-epithelial and epithelial levels of GM protection, while the post-epithelial level (production of vasodilating molecules NO and H_2S) was practically unaffected by this derivative, unlike meloxicam, which caused damage at all levels of protection. The obtained data supplement the data on the pharmacodynamics of the 4-methyl-2.2-dixo-1H-2λ^6,1-benzothiazine-3-carboxylic acid derivative and determine the expediency of its further studies as a potential non-opioid analgesic.

Keywords: *N-(4-methoxybenzyl)-4-methyl-2,2-dioxo-1H-2λ^6,1-benzothiazine-3-carboxamide, ulcerogenic effect, gastric mucosa, biochemical markers, oxidative stress, nitrogen monoxide, hydrogen sulfide.*

Introduction

Analysis of the pharmaceutical market of drugs shows that in the arsenal of modern non-narcotic drugs with pronounced analgesic and anti-inflammatory activity an important place belongs to the derivatives of carboxylic acids [9, 16]. According to the chemical structure, drugs of this class can be divided into several groups: first of all - derivatives of well-known salicylic acid (aspirin, etc.), derivatives of anthranilic and 2-aminonicotinic acids, which have structural similarity to salicylic acid (mefenamic, flufenamic acid, etc.). Particularly popular analgesics have been developed based on phenylacetic acid (diclofenac). In addition, the largest group of drugs approved for use as analgesics were 2-phenylpropionic acids (naproxen, dexketoprofen, ibuprofen). Separate mention should be made of derivatives of succinic acid (fenbufen and suxibuzone), hetarylic acid (etodolac and ketorolac), and hetarylacetic acid (indomethacin, sulindac). All of these drugs are the most common group of over-the-counter drugs used by more than 30 million people worldwide, despite the well-known class-specific gastrointestinal side effects (GIs) associated with the free carboxyl group. However, there is no doubt that the presence of an acid fragment (or chemical group that can be easily converted to such in vivo), often has a very positive effect on the

biological properties of a molecule [18]. Therefore, carboxylic acids are always of particular interest for the search for promising analgesics [22], and their possible side effects can be eliminated by subsequent chemical transformations into labile non-acidic groups or special conditions of their introduction [12].

Given the above, our attention was drawn to new derivatives of 4-methyl-2.2-dixo-1H-2λ^6.1-benzothiazine-3-carboxylic acid, in particular N-4-methoxybenzyl-amide - a substituted derivative (compound with laboratory code NI-9), which demonstrated high anti-inflammatory and analgesic activity in various models of pain perception [21]. Because this compound is derived from a bioisoteric substitution in the molecule of oxycamins, known nonsteroidal anti-inflammatory drugs (NSAIDs), in addition to establishing its pharmacological activity, it was necessary to conduct a study of the safety of this molecule in the gastrointestinal tract.

The aim of the study was to determine the effect of a new original derivative of 4-methyl-2.2-dixo-1H-2λ^6.1-benzothiazine-3-carboxylic acid on the macroscopic state and biochemical parameters of the gastric mucosa of rats.

Materials and methods

The research was performed on the basis of a research laboratory for preclinical study of pharmacological substances of the Department of Pharmacology of National Pirogov Memorial Medical University, Vinnytsya (certificate of the Ministry of Health on technical competence №030/18 dated November 1, 2018, valid until October 31, 2023). The study included 51 male Wistar rats obtained from the vivarium of the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine. During the experiment, the animals were kept in standard conditions (day/night regime 12/12 and access to water and food ad libitum), according to the norms. The research met all the necessary requirements for humane treatment of experimental animals and complied with the rules of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986) and current laws of Ukraine. Compound NI-9 and the most chemically similar drug meloxicam were administered intragastrically once daily for 28 days at a conditionally effective antinociceptive dose (ED50) of 3 and 5 mg/kg, respectively. Evaluation of ulcerogenic action of compounds by macroscopic signs was performed after euthanasia of animals by cervical dislocation, followed by dissection of the abdominal cavity, removed the stomach, cut at low curvature, washed with saline and assessed the degree of damage to the gastric mucosa. 0 - no damage; 0.5 - hyperemia; 1 - single minor injuries; 2 - multiple injuries (erosions, punctate hemorrhages); 3 - significant and multiple damage to GM; 4 - serious injuries (massive hemorrhages, erosions, perforations). The multiplicity of damage was estimated as the average number of ulcers per animal, the severity - was calculated as the average sum of the products - (the number of ulcers x severity). Ulcer index (UI) was calculated by the formula [19]: UI = arithmetic mean of the sum of points x% of animals with ulcers / 100.

During biochemical studies, GM was isolated, perfused with cold 1.15 % KCl solution and homogenized at 3000 rpm (Teflon glass) in 1.15 % KCl medium (1: 3 ratio). The protein content in the postnuclear supernatant was assessed by the microbiuret method [10], the level of malonic dialdehyde (MDA) - by reaction with thiobarbituric acid [23], carbonyl groups of proteins (CGP) - by reaction with 2,4-dinitrophenylhydrazine [20]. The level of glycosaminoglycans (GAG) was determined by the level of hexosamines by reaction with para-dimethylbenzaldehyde [14]. The content of phospholipid fractions was determined by thin layer chromatography on silica gel L5 / 40 (Chemapol, Czech Republic) using chloroform-methanol-water solvents in the ratio 65: 30: 5 (by volume). The phospholipid fractions of phosphatidylcholine (PH), lysophosphatidylcholine (LPH), phosphatidylethanolamine (PE) were identified by qualitative reactions and by Rf values, and their quantitative content was determined after chromatography by reaction with phosphorus-vanillin reagent.

The content of nitrites and nitrates was determined by reaction with Gris reagent [11]. The content of H_2S in blood serum was determined by spectrophotometric method, which is based on the formation of thionine in the reaction between sulfide anion and para-phenylenediamine hydrochloride in an acidic environment in the presence of iron (III) ions [29].

Statistical processing of the obtained results was performed by methods of variation statistics using the software package STATISTICA 10.0 with the calculation of the mean value, standard error of the mean, confidence interval (p) and non-parametric Mana-Whitney test. Differences were considered plausible in the case of $p<0.05$.

Results

Our results showed that long-term administration of the compound under study did not cause changes in eating behavior, appearance of rats and did not lead to death. Weight gain in animals administered NI-9 was 11.3±1.2 %, which was almost the same as in the meloxicam group (11.4±0.6 %). Body weight in control rats increased by 13.7±1.5 % during this period, but these differences were not significant. Analyzing the macroscopic picture of the gastric mucosa, it should be noted that the compound NI-9 caused less pronounced damage to GM than the comparison drug. Its long-term (28-day) administration caused ulcerative lesions was observed in only 71.4 % of animals against 85.7 % in the group administered meloxicam. The multiplicity of ulcers on the background of the introduction of a derivative of 4-methyl-2,2-dixo-1H-2λ^6,1-benzothiazine-3-carboxylic acid was 54.2 %, and the

severity was 30.8 % lower than that of the reference drug (Table 1). The ulcer index of compound NI-9 was 1.73 times lower than that of meloxicam.

The next step was to evaluate changes in biochemical markers of gastric mucosa in rats against NI-9 and meloxicam compared to control animals. The results showed that both compounds had a negative effect on the production of mucus in the stomach, as evidenced by a decrease in the content of glycosaminoglycans in GM (Table 2). However, against the background of the carboxamide derivative, the decrease in this indicator was 11.2 % relative to the control, while in animals administered meloxicam, this indicator decreased more markedly (by 21.1 %, $p<0.05$).

It is known that the basis of ulcerogenic action of NSAIDs is the development of oxidative stress in the gastric mucosa. Therefore, we further evaluated the changes in the products of lipid and protein peroxidation against the background of the action of the compounds studied. The results shown in Table 2 showed that NI-9 significantly increased the content of MDA and CGP in GM by 2.7 % and 14.3% compared to control rats, but this increase was 12.7 % and 11.9 % lower than in the background introduction of a reference drug ($p<0.05$).

Under the conditions of the experiment, the phospholipid spectrum of GM cell membranes also changed. Compound NI-9 caused a statistically significant decrease in the content of total phospholipids and phosphatidylcholine (by 13.5 % and 29.9 %, respectively $p<0.05$), with a simultaneous increase in the content of lysophosphatidylcholine and phosphatidylethanolamine by 22.2 % and 19.0 %, respectively, $p<0.05$). These values were smaller than the changes that meloxicam caused, but this difference did not reach statistically significant values (Table 3).

It is well known that violations of the integrity of the gastric mucosa on the background of NSAIDs are disorders of microcirculation, which lead to a prevalence of vasoconstrictor effects and reduced production of vasodilating molecules, in particular, nitrogen monoxide. Therefore, we further evaluated the total content of nitrates and nitrites in the GM under the conditions of administration of the compound NI-9 in comparison with meloxicam (Table 4).

Studies have shown that the use of a typical representative of the group of selective PTGS2 inhibitors meloxicam is accompanied by a significant reduction of NO_2^-+NO_3^- in GM by 20.6 %, respectively, while 28-day administration of NI-9 - did not change the content of these molecules in the stomach. A similar trend was found for the content of hydrogen sulfide - a vasoactive molecule that regulates the integrity of GM and plays an important protective role in NSAID-induced gastropathies [26]. It was found that the new derivative of benzothiazine-3-carboxylic acid had no depressant effect on the content of H_2S in CO, but on the contrary, showed a tendency to increase its content (by 3.57 %) compared with the control. At the same time, meloxicam probably (by 17.3 %) reduced the content of this vasodilator in the gastric mucosa.

Table 1. Indicators of gastrotoxicity of the compound NI-9 and meloxicam under conditions of long-term administration in rats (M±m, n=10).

	Plurality	Difficulty	Ulcerative index
Control	0	0	0
Compound NI-9 (3 mg/kg)	1.143±0,204*	0.857±0.161*	0.642
Meloxicam (5 mg/kg)	2.429±0,371	1.286±0,186	1.112

Note: * - statistically significant differences ($p<0.05$) relative to meloxicam.

Table 2. The effect of NI-9 compound and meloxicam on the level of lipid and protein peroxidation products in intact rats GM (M±m, n=7).

№ in order	Groups of rats	GAG, mg/g tissue	MDA, nmol/mg protein	CGP, nmol/mg protein
1	Control	4.047±0,113	6.485±0.225	2.430±0.090[!]
2	Meloxicam	3.251±0.102*	9.236±0.304*	3.174±0.131*
3	Compound NI-9	3.660±0.139*#	8.089±0.371*#	2.789±0.083*#

Notes: * - $p<0.05$ relatively intact animals; # - $p<0.05$ between groups of animals treated with meloxicam and compound NI-9.

Table 3. Effect of NI-9 compound and meloxicam on the phospholipid spectrum of intact rats GM (M±m, n=7).

№ in order	Phospholipid level, μg/mg protein	Groups of rats		
		Control	Meloxicam	Compound NI-9
1	General PL	274.8±8.302	222.3±7.800*	238.1±5.771*
2	PH	119.7±5.906	78.59±4.212*	84.11±3.892*
3	PE	64.80±4.837	80.40±4.521*	79.20±4.351*
4	LPH	18.91±1.219	23.40±1.285*	22.49±1.088*

Note: * - $p<0.05$ relatively intact animals.

Table 4. The effect of NI-9 compound and meloxicam on the content of hydrogen sulfide and metabolites of nitrogen monoxide in intact rats GM (M±m, n=7).

№ in order	Groups of rats	H_2S, nmol/mg protein	NO_2^-+NO_3^-, nmol/g of tissue
1	Control	1.637±0.085	2.103±0.147
2	Meloxicam	1.390±0,065*	1.700±0.148*
3	Compound NI-9	1.740±0.093#	2.200±0.166#

Notes: * - $p<0.05$ relative to intact animals; # - $p<0.05$ between groups of animals treated with meloxicam and compound NI-9.

Discussion

Studies have confirmed that the new original derivative of N-(4-methoxybenzyl)-4-methyl-2.2-dixo-1H-2λ⁶.1-benzothiazine-3-carboxylic acid - a compound with the laboratory code NI-9 - has a sufficient safety profile, and in its effect on the gastric mucosa is superior to the nearest chemical structure of the drug meloxicam. This is evidenced by a lower ulcer index of this compound with prolonged administration to the body in an average therapeutic dose of ED50 (3 mg / kg).

Specific gastric lesions, which include non-ulcer dyspepsia, epigastric pain, anorexia, esophagitis, constipation and diarrhea, erosions and ulcers in the stomach and duodenum, as well as perforation, have become clinically defined and are now referred to as "NSAID-gastropathy" [1, 2, 15, 17, 27]. These lesions mainly affect the stomach and duodenum, although NSAIDs can affect any part of the gastrointestinal tract, from the esophagus to the colon. The largest lesions are ketorolac, aceclofenac, celecoxib, desketoprofen, meloxicam, nimesulide and rofecoxib. The risk of bleeding was increased in patients with a history of peptic ulcer disease and/or gastrointestinal bleeding and using antiplatelet agents.

Nonsteroidal anti-inflammatory drugs are usually able to disrupt the integrity of the gastric mucosa due to the impact on different levels of its protection [6]. The main pre-epithelial (mucosal bicarbonate-phospholipid "barrier", creating cells of the superficial epithelium of the stomach, which produce mucus, bicarbonates, phospholipids, peptides, heat shock proteins, and some other biologically active substances that neutralize and disperse gastric lumen to mucous cells); epithelial (resistance of the surface of epithelial cells and intercellular contacts to the back diffusion of hydrogen ions and hydrophobic properties of the mucous membrane, which contribute to the "repulsion" of hydrochloric acid, as well as the high proliferative capacity of epithelial cells) and postepithelial, which are provided by vasoactive molecules. The most well-known components in this regard are prostaglandins (PG) - PGE2 and PGI2. According to modern ideas, their protective effect on the central nervous system is realized through several mechanisms: inhibition of hydrochloric acid in the stomach, increased secretion of mucus and bicarbonate, and PGI2 (prostacyclin), is a powerful vasodilator that provides normal blood circulation in the gastric mucosa, stabilizes the membranes of mast cells and lysosomes, inhibits the production of free radicals and enzymes by neutrophils, regulation of vascular endothelium.

Microcirculation disorders due to hyperproduction of vasoconstrictor and decrease in the content of vasodilating molecules play an important role in the biochemical mechanisms of development of NSAID-induced gastric lesions. The literature describes a number of biologically active substances of endothelial and plasma origin, which regulate vascular tone. Among these mediators, in addition to prostaglandins, oxygen free radicals, nitric oxide, and H_2S have recently been identified [4, 13, 24, 25, 28]. Therefore, the search for and research of new drugs that have anti-inflammatory and analgesic activity, it is necessary to establish their safety in the gastrointestinal tract.

The results obtained in our study showed that among the molecular mechanisms of modulation of the GM on the background of the compound NI-9, we can note its negative impact on the processes of lipid and protein peroxidation, mucus production, phospholipid spectrum of GM cell membranes, the severity of which meloxicam. In addition, it should be noted that in contrast to the latter, the derivative of benzothiazine-3-carboxylic acid has no inhibitory effect on the production of nitrogen monoxide, and also tends to increase the content of hydrogen sulfide in the GM, which may have been one of the explanations for its greater stomach safety.

The reason for such differences, in our opinion, may be the peculiarities of the chemical structure of this molecule. It is known from the literature that one of the prerequisites for the safety of NSAIDs in the gastrointestinal tract is a selective effect on PTGS2 and the absence or minimal effect on PTGS1. Meloxicam, as the closest in structure to NSAIDs, belongs to a group of drugs that mainly affect the inducible isoform of cyclooxygenase [3, 7]. The drug binds to the upper part of the PTGS2 channel and has a balanced PTGS2 selectivity profile. Other highly selective PTGS2-coxib inhibitors also do not have the ability to damage the stomach, however, they bind to the lateral pocket of the PTGS2 channel and inhibit thromboxane less, which explains the increased risk of thromboembolic complications if long-term use [5]. It is possible that the N-(4-methoxybenzyl)-4-methyl-2.2-dixo-1H-2λ^6.1-benzothiazine-3-carboxylic acid derivative studied has its own interactions with molecular markers of inflammation and pain. However, for final conclusions it is necessary to conduct additional research in this direction.

Conclusion

The data obtained show, that compound N-(4-methoxybenzyl) -4-methyl-2.2-dixo-1H-2 λ^6.1-benzothiazine-3-carboxylic acid has a high degree of safety in relation to the gastrointestinal tract in intact, which exceeds reference preparation meloxicam. This difference is mainly due to a less pronounced depressant effect on the postpithelial mechanism of protection of the gastric mucosa, namely, the production of vasodilating molecules in the central nervous system. The results supplement the data on the pharmacodynamics of the 4-methyl-2.2-dixo-1H-2λ^6.1-benzothiazine-3-carboxylic acid derivative and determine the feasibility of its further studies as a potential non-opioid analgesic.

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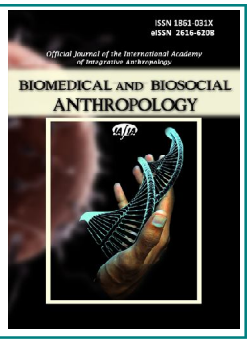

Changes in the histostructure of the lungs of old rats under conditions of persistent hyperhomocysteinemia

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To date, homocysteine has been found to be an important biomarker of bronchopulmonary pathology, including COPD. The increase in its concentration in the blood plasma causes the start of free radical processes and the production of reactive oxygen species, which activate lipid peroxidation in lung tissue. In addition, the activation of endoplasmic reticulum stress with increasing homocysteine levels is the main reason for triggering apoptosis of alveolocytes. The aim of the research is to study the features of lungs histostructure in old rats under conditions of hyperhomocysteinemia. The experimental study was performed on 20 white nonlinear old (24-26 months) male rats. During the experiment, the animals were divided into two groups - control and experimental. Simulation of the state of persistent hyperhomocysteinemia was achieved by administering to rats of experimental group thiolactone homocysteine at a dose of 200 mg/kg body weight intragastrally for 60 days. Histological specimens were studied using an SEO CCAN light microscope and photo-documented using a Vision CCD Camera with an image output system from histological specimens. In elderly animals under conditions of experimental hyperhomocysteinemia develop severe destructive-degenerative changes in the lungs. Significant remodeling of the vascular bed, bronchi, inflammatory manifestations, enlargement of dis- and atelectasis and emphysematically altered alveoli of the respiratory lungs, violation of the alveolar walls, with the release of blood cells into the alveolar space and the formation of small diapedetic hemorrhages. The development of perivascular, peribronchial and interstitial sclerosis is characteristic.

Keywords: *hyperhomocysteinemia, atelectasis, emphysema, sclerosis.*

Introduction

Homocysteine is a natural metabolite formed from the amino acid methionine. Under normal conditions, its level in blood plasma is about 5-15 μmol/l [15]. However, disorders of homocysteine metabolism, characterized by an increase in its concentration above 15 μmol/l, causes the development of hyperhomocysteinemia syndrome. The latter, according to the literature, is closely correlated with pathologies of the cardiovascular and respiratory systems, thrombotic complications, neurodegenerative processes, etc. [1, 21]. Thus increase in level of homocysteine in blood, in the specified conditions, can be both the reason, and a consequence of the listed pathological states. Increased homocysteine concentration occurs when the synthesis of methionine and cysteine, which develops due to deficiency of vitamins B6, B9 and B12, as well as genetic polymorphism of certain enzymes - methylenetetrahydrofolate reductase, cystathionine-β-synthase [4, 9, 13, 17].

The pathogenesis of the negative impact of hyperhomocysteinemia on the human body is being actively studied. Thus, for a number of decades it is undeniable that elevated levels of homocysteine are one of the main risk factors for the occurrence and progression of numerous pathological conditions. It is known to damage endothelium walls of blood vessels, activates the blood coagulation system, increases the myotoxicity of smooth muscle cells, interacts and competes with glutamate receptors of neurons, megakaryocytes, erythrocytes, lymphocytes, neutrophils, cardiomyocytes. In addition, hyperhomocysteinemia is associated with the development of oxidative stress, inflammation and fibrosis [3, 5, 7].

The influence of homocysteine on the peculiarities of the histostructure of the respiratory system is still insufficiently studied. However, to date, it has been established that it is an important biomarker of bronchopulmonary pathology,

including COPD. The increase in its concentration in blood plasma causes the start of free radical processes and the production of reactive oxygen species, which in lung tissue activate lipid peroxidation due to the presence of a significant amount of unsaturated fatty acids. It is also known that homocysteine is able to affect the structure and function of proteins through the process of their homocysteine. The latter occurs during post-translational modifications of proteins in the endoplasmic reticulum and can cause misfolding, organelle overload and the development of stress. Stress of the endoplasmic reticulum in lung tissue under conditions of hyperhomocysteinemia triggers signaling pathways of cell apoptosis, so it is a common cause of alveolocyte death [11, 14, 19].

At present, domestic and foreign scientometric sources have an extremely limited number of studies on histological changes in lung tissue in hyperhomocysteinemia, and some fragmentary data do not fully outline this problem.

The aim of the research is to study the features of the histostructure of the lungs of old rats under conditions of hyperhomocysteinemia.

Materials and methods

The experiments were performed on 20 white nonlinear old (24-26 months) male rats. During the experiment, the animals were divided into two groups - control and experimental. Simulation of persistent hyperhomocysteinemia was achieved by administering to rats the experimental group of thiolactone homocysteine at a dose of 200 mg/kg body weight intragastrally for 60 days [16]. Animals were decontaminated by decapitation under thiopental anesthesia [6]. For microscopic examination, pieces of lungs were taken from pre-weighed animals of all groups. The pieces were fixed in 10% formalin solution, while the duration of exposure did not exceed 1 - 2 days. The applied fixing solution prevents the process of autolysis and stabilizes cells and tissues for their further processing and use in staining procedures. Next, the pieces were dehydrated in alcohols of increasing concentration and poured into paraffin blocks. The sections made with a thickness of 4 - 5 μm were stained with hematoxylin and eosin and methylene blue [2, 10]. Histological specimens were studied using an SEO CCAN light microscope and photo-documented using a Vision CCD Camera with an image output system from histological specimens.

Results

Microscopic examinations of the lungs of experimental animals of old age on the background of hyperhomocysteinemia revealed significant inflammatory, destructive changes and characteristic sclerotic changes of blood vessels, bronchi, respiratory tract. Changes in the bronchi were characterized by remodeling of all wall membranes. The mucous membrane undergoes significant alternative changes, in the epithelial plate the cells had fuzzy membranes of plasmalemma, dystrophically altered, enlightened

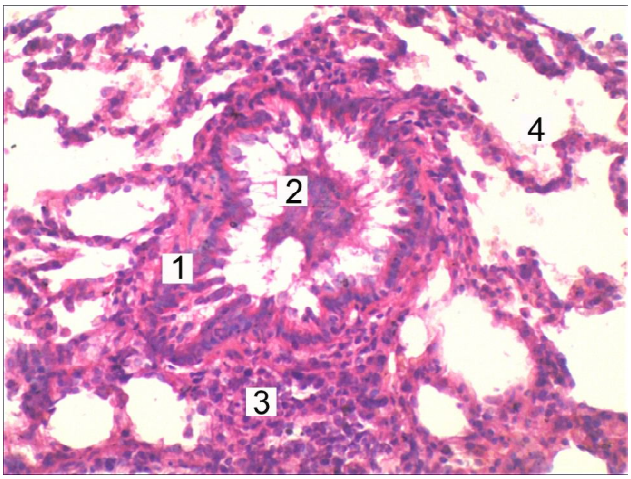

Fig. 1. Microscopic changes in the lungs of an elderly animal under conditions of hyperhomocysteinemia. Deformed bronchial wall (1), mucosal detritus in the lumen (2), leukocyte infiltration of the adventitia (3), respiratory department (4). Staining with hematoxylin and eosin. x200.

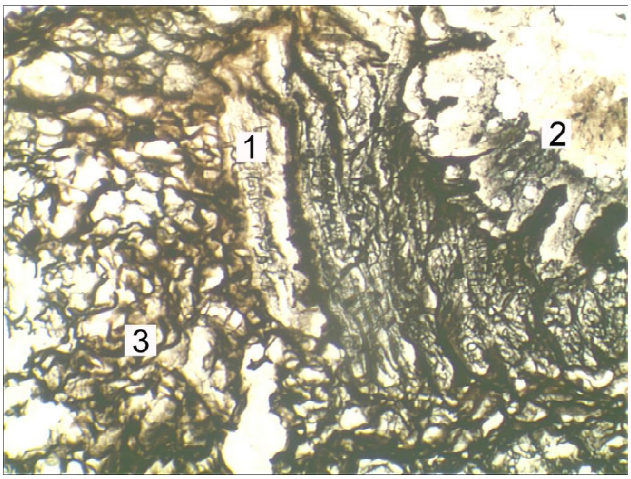

Fig. 2. Microscopic condition of the lung of an old rat impregnated with silver nitrate under conditions of hyperhomocysteinemia. Disorganization of reticular fibers of the bronchial wall (1), lumen with mucous content (2), argyrophilic collagen fibers of adventitia (3). Gordon and Sweets staining method x200.

cytoplasm, hyperchromic, pyknotic nuclei. Desquamation of epitheliocytes into the bronchial lumen was determined. The bronchi were deformed due to atrophy or hypertrophy of the muscle plate, especially the small bronchi and bronchioles, and due to inflammatory and sclerotic changes. Volumetric accumulations of mucosal detritus were determined in their lumens (Fig. 1).

Impregnation with silver salts reveals an increase in the content of fibrous components in the bronchial wall, especially the adventitial membrane, which have intense argyrophilia, which leads to peribronchial sclerosis (Fig. 2).

Histologically at this time of the experiment it was found that the vessels are characterized by moderate blood supply, but often found in the lumens formed clots. The wall is destructively changed, deformed. In the endothelium of the

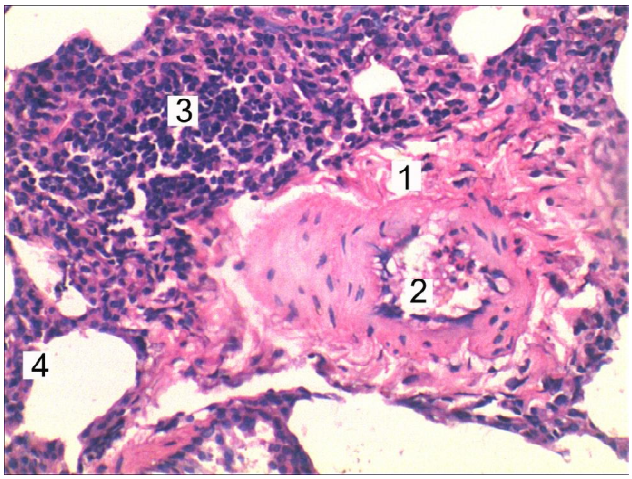

Fig. 3. Histological changes in the lungs of an elderly animal under conditions of hyperhomocysteinemia. Dystrophically altered artery wall (1), lumen (2), leukocyte infiltrate (3), respiratory tract (4). Staining with hematoxylin and eosin. x200.

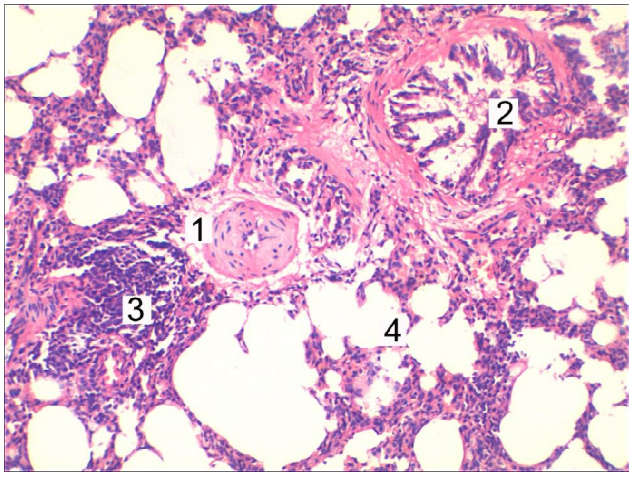

Fig. 4. Histological changes in the lungs of an elderly animal under conditions of hyperhomocysteinemia. Artery of small caliber "closing type" with hypertrophy of the media (1) deformed, destructively altered bronchus (2), leukocyte infiltrate (3), respiratory department (4). Staining with hematoxylin and eosin. x100.

intima there are deformation, homogenization of the inner elastic membrane, pyknosis of endothelial nuclei and desquamation into the lumen of the vessel of endothelial cells with the exposure of the basement membrane. Smooth media myocytes are swollen, homogenized, dystrophically altered, contain hyperchromic nuclei. There are small vessels in the body, the so-called "closing" arteries, in which the media is thickened due to hyperplasia of smooth muscle cells, the lumen of which is narrow, slit-like (Fig. 3). Manifestations of the inflammatory nature of the vascular wall were determined by leukocyte infiltration of the entire thickness, mostly adventitia (Fig. 4).

Also during this period of the experiment revealed pronounced manifestations of sclerosis of the wall, mostly adventitia, which was manifested by active proliferation of fibroblasts and the growth of reticular and, to a greater extent, collagen fibers, which have a bright argyrophilia (Fig. 5).

The vessels of the hemomicrocirculatory tract were also significantly altered, manifested by heterogeneity. Venules were characterized by stagnation, stasis, erythrocyte sludge, thrombosis. Endotheliocytes are dystrophically altered, contain pyknotic nuclei that protrude into the lumen of the vessel. The arterioles had a thickened, destructively altered wall and a narrowed, spasmodic lumen. Significant perivascular leukocyte infiltration was detected. Hemocapillaries are also characterized by plethora, stasis and sludge, the basement membrane is homogeneous, swollen, indistinctly contoured, dystrophically altered endothelium.

Reorganization of vessels and bronchi is accompanied

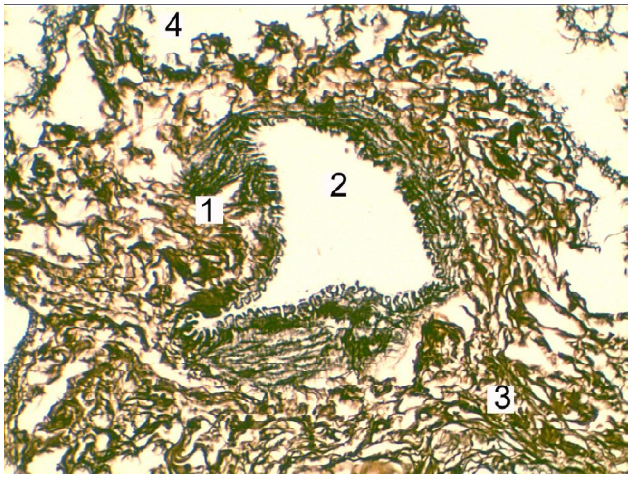

Fig. 5. Microscopic condition of the lung of an old rat impregnated with silver nitrate under conditions of hyperhomocysteinemia. Deformation and destruction of the artery wall (1), lumen of the vessel (2), argyrophilic collagen fibers of the adventitia (3), respiratory department (4). Gordon and Sweets staining method. x200

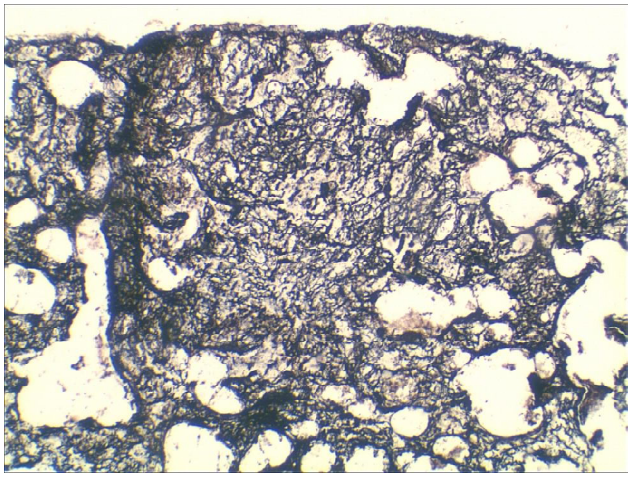

Fig. 6. Microscopic condition of the lungs of old rats when impregnated with silver nitrate under conditions of hyperhomocysteinemia. Growth in the respiratory department of small argyrophilic reticular and collagen fibers. Gordon and Sweets staining method. x100.

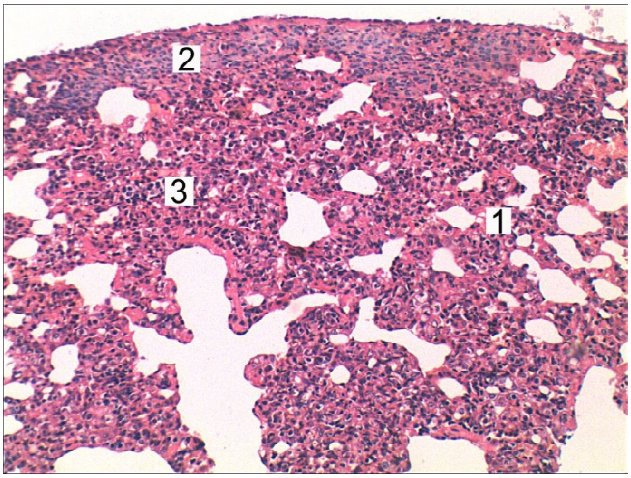

Fig. 7. Histological changes in the lungs of an elderly animal under conditions of hyperhomocysteinemia. Areas of dis- (1) and atelectasis (2), with leukocyte infiltration (3). Staining with hematoxylin and eosin. x200.

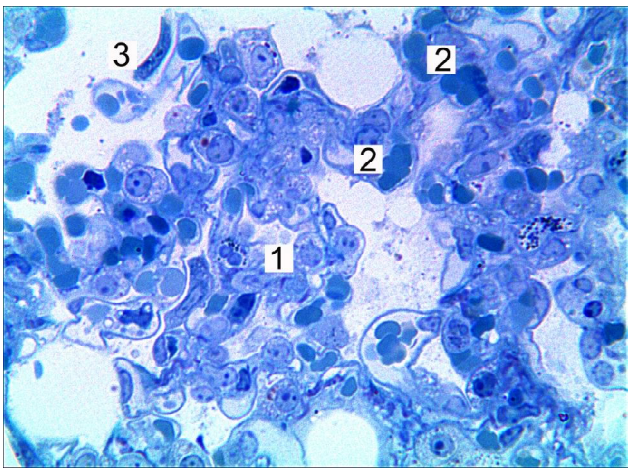

Fig. 8. Microscopic changes in the lungs of an elderly animal under conditions of hyperhomocysteinemia. Areas of dis- and atelectasis (1), blood-filled hemocapillaries (2), alveolar macrophages (3) of the respiratory department. Semi-thin slice. Methylene blue staining. x400.

by changes in the parenchyma of the organ. Lung tissue is heterogeneous, dominated by areas of dis- and atelectasis, which show the growth of collagen fibers, which are clearly defined by impregnation with silver salts, which leads to widespread mosaic fibrosis of the respiratory tract (Fig. 6). Emphysematically dilated alveoli are present mainly in the subpleural areas. Areas of unchanged histostructure of lung tissue are relatively small. Areas of damage to the interalveolar septa are detected, with the release of formed blood elements into the lumen of the alveoli. There are small interstitial and focal hemorrhages.

Histo-leukocyte infiltration is present in almost all fields of view in the components of the respiratory department of the lungs (Figs. 7, 8). Numerous young and actively phagocytic macrophages were found in the lumens of the alveoli.

Discussion

In the modern world, interest in the problem of hyperhomocysteinemia and its importance in the mechanisms of occurrence and progression of diseases of the respiratory system is growing significantly. In recent years, numerous clinical studies have shown that homocysteine is a predictor of COPD. A significant increase in its concentration in the blood causes a worsening of the disease, the development of complications or comorbid pathologies, mainly from the cardiovascular system. The causes of hyperhomocysteinemia in COPD are not clearly established, but it is characteristic that this group of patients is deficient in vitamins B6, B9 and B12, which act as important cofactors in biochemical reactions of homocysteine utilization. According to scientists, one of the mechanisms of pathogenetic action of homocysteine under these conditions is the development of oxidative stress. This fact is explained by the significant depletion of the antioxidant defense system, which in patients manifests itself in the form of a significant decrease in the levels of reduced and total glutathione [12].

According to other authors, not only the level of homocysteine but also the balance in the H_2S / homocysteine system plays an important role in the course of diseases of the respiratory system. It is known that H_2S has anti-inflammatory, antioxidant properties, prevents the development of fibrosis and damage to lung tissue. Patients with bronchopulmonary pathology show a decrease in the concentration of H_2S, and its levels are negatively correlated with the severity of the disease. Under these conditions, the presence of risk factors such as overweight, dyslipidemia, smoking, old age and hyperhomocysteinemia create the basis for the activation of free radical processes and the development of oxidative stress. A significant increase in the concentration of homocysteine is the cause of inflammatory processes in the smooth muscle cells of vascular walls, endothelial damage. These changes not only worsen the course of the disease, but also become the basis of severe cardiovascular complications, including heart attacks or strokes [8].

Recent studies on mice have shown that persistent experimental hyperhomocysteinemia combined with exposure to animal smoke is the cause of severe pulmonary emphysema, which is seen in histological studies as significant alveolar cell death. The latter is probably due to the triggering of endoplasmic reticulum stress and apoptosis signaling pathways [18].

It is also relevant that hyperhomocysteinemia and vitamin B9 deficiency are considered risk factors for lung cancer. According to researchers, the pathogenesis of this phenomenon is a violation of DNA methylation. One of the important donors of metal groups is S-adenosylmethionine, but its level is significantly reduced under conditions of folate deficiency, changes in the mechanisms of homocysteine metabolism and, accordingly, an increase in the concentration of the latter.

There is a violation of methylation of cytosine in DNA, violation of oncogene suppression and activation of malignant cell transformation [20].

Conclusion

In elderly animals under conditions of experimental hyperhomocysteinemia develop severe destructive-degenerative changes in the lungs. Significant remodeling of the vascular bed, bronchi, inflammatory manifestations, enlargement of areas of dis- and atelectasis and emphysematically altered alveoli of the respiratory lungs, violation of the alveolar walls, with the release of blood cells into the alveolar space and the formation of small diapedes. Activation of fibroblasts is manifested by a pronounced collagen formation, which causes perivascular, peribronchial and interstitial sclerosis, which has a significant negative impact on the process of gas exchange in the lungs.

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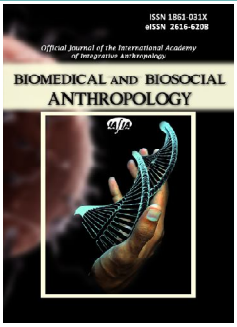

Investigation of pharmacokinetics of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide various crystalline modifications in vivo

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The phenomenon of polymorphism, inherent in many biologically active substances, including drugs, is an extremely serious problem that requires close attention and comprehensive study. Various crystalline modifications of biologically active compounds, as well as excipients can dramatically change the biopharmaceutical properties and pharmacological characteristics of already known drugs. The bioactive compound N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide was obtained by bioisosterical substitution in the molecule of known non-steroidal anti-inflammatory drugs of the oxycam group in the form of three polymorphic modifications of the crystal. sticks (form A), plates (form B) and blocks (form C) with varying degrees of analgesic and anti-inflammatory effects. The aim of the study was to investigate the pharmacokinetic profile of these polymorphic forms of benzothiazine-3-carboxamide derivative by their oral administration in vivo. The concentration of compounds in the blood of mice was determined by HPLC and the main pharmacokinetic parameters were calculated. It was found that the polymorphic form in the form of plates (form B), in particular, having the largest surface area of crystals, has differences mainly at the stage of absorption with corresponding changes in absorption values, maximum concentration and time of its achievement, has the highest bioavailability and rapid elimination which correlates with the most optimal pharmacological and toxicological characteristics of this compound in comparison with other crystalline forms. This makes it possible to recommend the most active and safe polymorphic form of the compound (form B) for in-depth preclinical study and possible clinical trials as an analgesic and anti-inflammatory agent.

Keywords: *N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide, polymorphic modifications, crystal habitus, parameters of pharmacokinetic.*

Introduction

The phenomenon of polymorphism among biologically active substances occupies one of the leading places in the process of drug development and pharmaceutical development of the dosage form. To date, the phenomenon of polymorphism has been detected for more than 85 % of pharmaceutical substances and the process of relevant research continues [9]. The accumulation of experimental material and clinical experience has formed a clear understanding that polymorphism for pharmacy and medicine is an extremely serious and important problem that requires close attention and comprehensive study.

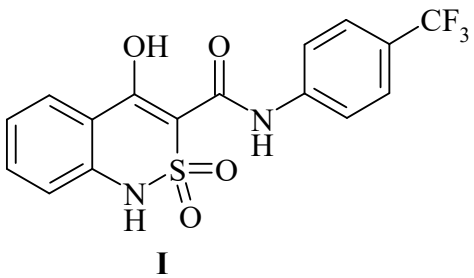

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Fig. 1. Chemical formula of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide.

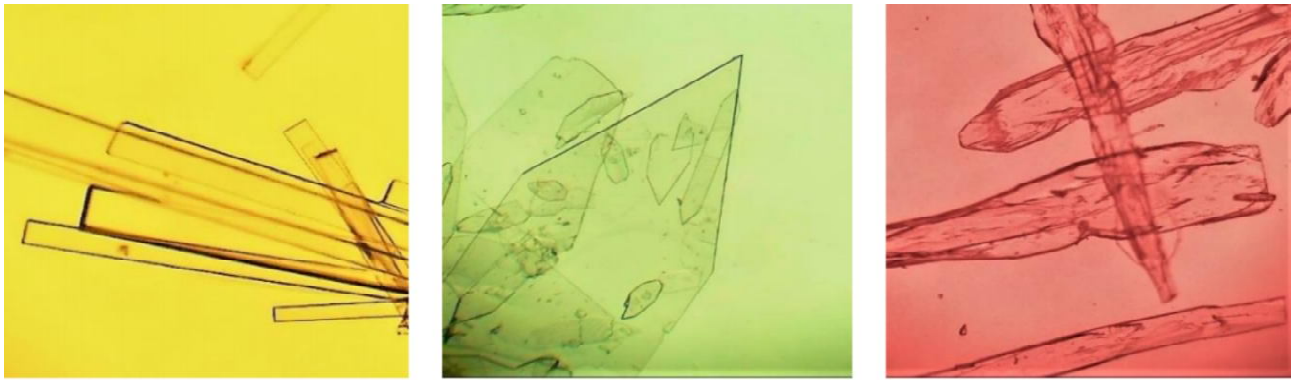

Fig. 2. Crystalline forms of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide, derived from ethyl acetate (A), meta-xylene (B) and ortho-xylene (C).

Various crystalline modifications of biologically active compounds, as well as their excipients can dramatically change (and not always for the better) technological, pharmaceutical and pharmacological characteristics of already known drugs [3, 7, 8, 15]. It is for these reasons that the phenomenon of pharmaceutical polymorphism is being actively studied and strictly controlled in many countries around the world [14].

The objects of the study were compounds - derivatives of 4-R-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxylic acids, synthesized by bioisosteric substitution in the molecule of oxicams at the Department of Pharmaceutical Chemistry of the National University of Pharmacy under the leadership of Professor Ukrayinets I. V. Preliminary results [16] proved the presence of derivatives of this chemical class of high analgesic activity and established a leader compound, namely N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide (Fig. 1).

In the process of chemical synthesis of this compound by crystallization from generally acceptable organic solvents (ethyl acetate, meta-xylene and ortho-xylene) three externally completely different types of completely colorless crystals were obtained - long sticks with a square cross section (form A), thin chisel-shaped plates (form B) or elongated blocks without a clear geometric shape (shape C), respectively (Fig. 2).

Detailed studies of their antinociceptive effects in five models of pain perception have shown that, despite their chemical identity, they differ significantly in the strength of the analgesic effect, as well as acute toxicity and gastric damage [19]. Therefore, the question arose to establish the reasons that may explain the existence of these differences.

The aim of the study was to investigate the features of the pharmacokinetic behavior of three crystalline modifications of the benzothiazine-3-carboxamide derivative by their oral administration in vivo.

Materials and methods

The study was performed on 156 white nonlinear male mice kept on a standard vivarium diet, access to water *ad libitum* and 12/12 day/night. All studies were performed in accordance with the requirements of the Helsinki Declaration on the Humane Treatment of Laboratory Animals and the current laws of Ukraine.

Determination of the content of the test compound was performed on a combined HPLC-MS system - liquid chromatograph 1260 Infinity with a detector 6530 Accurate Mass Q-TOF, "Agilent Technologies". The test compounds were administered orally at a dose of 10 mg/kg as a suspension stabilized with methylcellulose (0.5 %). At certain intervals after administration (0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 h), the animals were subjected to chloroform anesthesia and decapitated by collecting blood in centrifuge tubes. Blood samples were kept for 0.5 h at 37 °C, blood serum was separated by centrifugation (15 min, 6000 rpm). To 200 µl of serum was added 300 µl of a mixture of 7 % perchloric acid - acetonitrile (60:40) to precipitate proteins, stirred and centrifuged (8000 rpm, 5 °C, 20 min). The supernatant was filtered through a microporous filter (20 µm), the bridge of the test substance was determined by HPLC under these conditions with a sample injection volume of 20 µl. The calculation of the concentration of the compound in the serum (C, µg/cm^3) was carried out according to the formula:

$C=Q\ ((V_1+V_2)*1000)/(V_1*V_3)$,

where: Q is the amount of compound determined in the injection sample according to the calibration schedule; V_1 - serum volume, µl; V_2 - volume of perchloric acid solution with acetonitrile V_3 - volume of injection, µl; 1000 - conversion factor per 1 cm^3 [6, 17].

Statistical processing of the obtained results was performed by non-parametric methods using the software package STATISTICA 10.0 with the calculation of the mean value, standard error of the mean. Differences were considered plausible in the case of $p<0.05$.

Results

After oral administration of a benzothiazine-3-carboxamide derivative in the form of various polymorphic

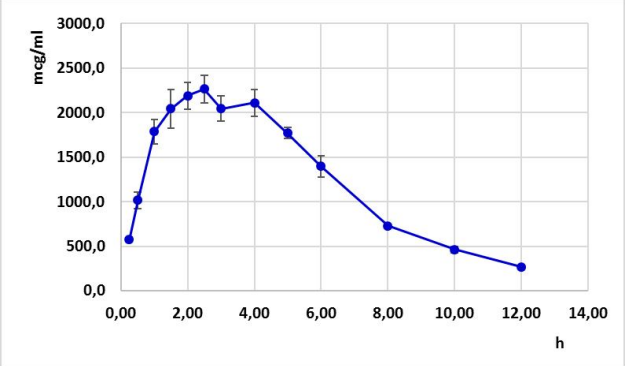

Fig. 3. Concentration profile of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide (A form) after its oral administration (10 mg/kg, M±m, n=4).

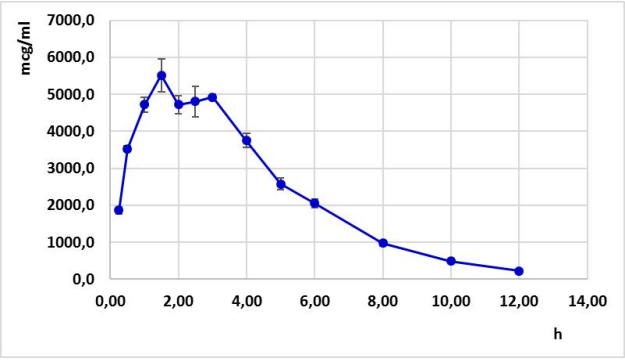

Fig. 4. Concentration profile of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide (B form) after its oral administration (10 mg/kg, M±m, n=4).

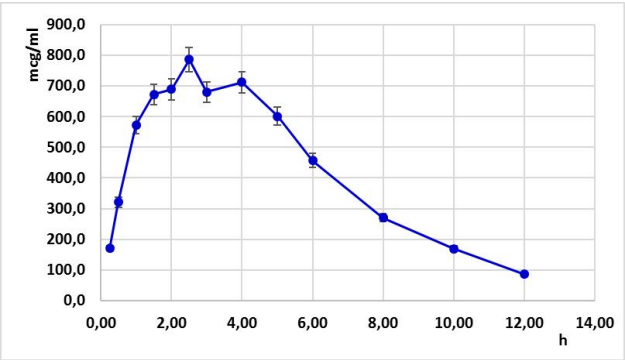

Fig. 5. Concentration profile of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide (C form) after its oral administration (10 mg/kg, M±m, n=4).

forms, its content in blood plasma is determined in rather high concentrations, and the concentration profile corresponds to the distribution kinetics according to the single-chamber model with absorption. It should be noted, however, that the type of concentration curves of the content of compounds A, B and C after administration in the form of polymorphic forms, are quite different both in profile and in the values of certain concentrations (Fig. 3-5). Thus, the introduction of polymorphic form B leads to higher concentrations of it in blood plasma (see Fig. 4) in comparison with the introduction of polymorphic form A (see Fig. 3). Also for polymorphic form B there is a narrower peak of reaching the maximum concentration with, respectively, higher levels of the compound in the blood plasma than for polymorphic form A. Regarding form C, its concentration profile (see Fig. 5) shows intermediate indicators, which resemble those that can be obtained by introducing a mixture of polymorphic forms A and B and inherent in the additivity of the processes of mass transfer of the compound in the body.

To quantify the pharmacokinetic processes of polymorphic forms, the corresponding pharmacokinetic parameters for polymorphic forms A, B and C were calculated after their single oral administration (Table 1).

It was found that the pharmacokinetic parameters that characterize the processes of distribution of the compound are quite similar for all three forms (see Table 1). The constant volume of distribution (V_{dss}) for polymorphic forms did not have a statistically significant difference, although the difference between form B and polymorphs A and C at the trend level was recorded. This demonstrates the lack of influence of polymorphic modification on the processes of compound distribution in the body.

The magnitude of the plasma elimination constant is usually due to the similarity of the physicochemical properties of the compound itself (water solubility, reactivity, binding to plasma proteins, etc.). Our results showed that the elimination constant for polymorphic form B when administered orally was 1.48 times higher compared to form A and C, and the half-life of form B was 34.7-31.6 % less than other polymorphic forms ($p<0.05$), which indicates about the higher rate of excretion of compound B from the body. These values are lower than those for the compound when administered intravenously, which was 0.511±0.068 h^{-1} (data not published), but the difference is not statistically significant and is probably due to the lack of absorption during intravenous administration. Another factor that leads to a partial decrease in the rate of elimination of the compound may also be a combination of active transport and passive diffusion in the overall elimination process, so that at high plasma concentrations the studied compound is excreted by both mechanisms, while at lower concentrations achieved after oral administration, a significant contribution is due only to active transport. Accordingly, the values of the half-life ($T_{el}^{1/2}$) of the compound from the body are also close.

The amount of total clearance, which depends on the volume of distribution and elimination of compounds in compound B, was also smaller compared to the other two forms (18-25 % on average), but this difference also did not reach probable values.

At the same time, it should be noted that the process of absorption of polymorphic forms is significantly different, which is reflected in the indicators of the corresponding pharmacokinetic parameters. First of all, it is noticeable (see Table 1) that the process of absorption of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide in polymorphic form B occurs

Table 1. Pharmacokinetic parameters of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide after its oral administration in the form of polymorphs A, B and C (10 mg/kg, M±m, n=4).

Pharmacokinetic parameter	A form	B form	C form
Absorption constant, k_{abs}, h^{-1}	0.669±0.067	0.750±0.077*/**	0.624±0.081
Elimination constant, k_{el}, h^{-1}	0.270±0.018	0.401±0.024*/**	0.274±0.017
Constant volume of distribution, V_{dss}, l/kg	6.000±1.310	4.610±0.476	5.612±1.421
Maximum concentration, C_{max}, mcg/ml	671.4±21.8	809.5±71.4*	786.1±10.1
Time to reach maximum concentration, T_{max}, h	3.000	1.500	2.510
Area under the pharmacokinetic curve, $AUC_{0-\infty}$, mcg*h/ml	4687±798	4281±586	5308±720
The area under the first moment of the pharmacokinetic curve, $AUMC_{0-\infty}$, mcg*h^2/ml	35529±8882	18495±1755	40152±3989
The average retention time in the body, MRT, h	7.581±0.286	4.322±0.719*	7.376±2.076
Total clearance, Cl_{tot}., l/kg*h	1.611±0.019	1.900±0.110	1.511±0.100
Semi-elimination time, $T_{el}^{1/2}$, h	2.621±0.210	1.712±0.119*/**	2.502±0.200
Half-absorption time, $T_{abs}^{1/2}$, h	1.042±0.112	0.919±0.093	1.110±0.142
Bioavailability, f	0.719± 0.063	0.810±0.178*/**	0.122±0.013

Notes: * - statistically significant differences ($p < 0.05$) to the form A; ** - statistically significant differences ($p < 0.05$) relative to form C.

with a much larger rate than in the form of polymorphic form A, because the absorption constant of form B statistically exceeds the same rate of compound A by 12.1 %, and compound C - by 20.2 %. Accordingly, the average half-absorption time ($T_{abs}^{1/2}$) is on average 11.5 % lower for polymorphic form B compared to the other two crystal forms. Shorter absorption time for form B causes a total shorter residence time of this compound in the body (by 43.0 %) compared to forms A and C. The rate of absorption and the ratio of absorption and elimination constants are also known to affect the value (C_{max}, μg/ml) and time (T_{max}, h) to reach maximum concentration. Polymorphic form B of the benzothiazine-3-carboxamide derivative shows a higher maximum concentration, which is 20.6 % higher than form A ($p<0.05$) and unreliable ($p>0.05$) of compound C, and the time to reach the maximum concentration of compound B was twice as fast as in form A (see table. 1).

Due to the higher rate of absorption of the compound N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide in the form of polymorphic form B, significantly increases the amount of substance entering the internal environment of the body - the integral value of the amount of compound entering the blood (area under the pharmacokinetic curve "concentration-time", $AUMC_{0-\infty}$) is 4281±586 μg*h^2/ml, while for form A - 4687±798 μg*h^2/ml.

The higher absorption rate also causes the expected increased bioavailability (f) for polymorphic form B - indeed, for form B this indicator was significantly higher by 12.5 and 24.6 % than for polymorphic forms A and C. This indicates that form B has greater bioavailability. due to the higher degree of absorption.

Discussion

Inherent in many substances, including biologically active, polymorphism is an extremely serious problem. The phenomenon of polymorphism is explained by the fact that the same atoms of matter can create different stable crystal lattices. This phenomenon was first described in 1788 by the German chemist Claport M.G. In 1942, more than 1,200 organic polymorphic compounds were known, now there are more than 10,000. Polymorphism of the active pharmaceutical substance (APS) can cause pharmaceutical inequality and, as a consequence, pharmacokinetic and therapeutic non-equivalence of drugs in solid dosage form. There are significant differences in the solubility of polymorphic modifications of APS can lead to differences in the kinetics of their dissolution in vivo and, as a consequence, the bioavailability of drugs. The bioavailability / bioequivalence of drugs depends on a number of factors that determine the rate and degree of their absorption, such as dissolution kinetics and penetration through cell membranes, gastrointestinal motility, metabolism. These factors are taken into account in the concept of biopharmaceutical classification system (BCS) APS, which is already accepted in the manuals of regulators in industrialized countries [1].

At present, polymorphism is found in more than 70 % of drugs in almost all pharmacological groups. It is an extremely important factor that modifies the therapeutic properties of pharmaceutical substances and dosage forms, significantly affects the parameters of their biological activity, as well as pharmacokinetics. Polymorphic changes in drugs can cause rapid inactivation of drugs, changes in the physical parameters of finished drugs, chemical incompatibility of ingredients in the same dosage form. By changing the pharmacokinetics of the drug, the polymorphism may affect its toxicity. Pharmaceutical substances have the ability to form polymorphic modifications that differ from each other in crystallographic parameters, physicochemical properties and the like.

Different in strength and toxicity, different polymorphs and stereoisomers are able to form antibacterial drugs (chloramphenicol, ampicillin, tetracycline), local anesthetics and analgesics (ibuprofen, ketoprofen), hormonal and cardiovascular drugs methylprednisolone, insulin, progesterone [2, 4, 9, 10, 11, 20].

However, in recent years, no less important characteristic that significantly affects the properties of biologically active substances and drugs, their habit (appearance) - needles, plates, cubes, prisms, shapeless crystals and others. Samples of the active substance may differ in the degree of wettability, compressibility, hygroscopicity, stability, solubility and other physicochemical properties, which ultimately affects the quality of the final product. That is why these moments are currently receiving a lot of attention [4, 5, 11, 12, 18, 20]. The crystalline modifications of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide presented in this work are unique in that they differ only in appearance, whereas the X-ray diffraction analysis showed their identical molecular and crystalline structure. These crystals differ only in some geometric characteristics of the studied molecules - the length of the connections, the angle of deviation of atoms and the total value of the valence angles [19]. Studies of biological activity in different models of pain perception have shown that these compounds differ in both strength and speed of onset of effect. Thus, under the conditions of oral administration in the model of acetic acid cramps in mice and thermal irritation of the tail (tail flick and tail emersion), the most powerful effect was shown by compound B, while compound A was significantly inferior in strength and compound C was intermediate. An in-depth study of the rate of onset and duration of analgesic effect, which was studied in a model of electrical irritation, showed that the effect of compound B occurs most rapidly, reaches a maximum at 2 hours, but then its effect gradually decreases. On the other hand, compound A, acts slowly with a maximum at the 4th hour, does not reach the level of compound B by force, but its duration of action is much longer than the last one. Based on the working hypothesis that such a difference is due to the different rate of absorption in the gastrointestinal tract and greater bioavailability of crystalline form B compared to the other two - was fully confirmed in this work. Given the route of administration of the compound, as well as the fact that it was administered as polymorphs and under conditions that preserve the crystal lattice, it can be assumed that the type of polymorph and its effect on the biopharmaceutical phase (dissolution after oral administration and subsequent absorption in the gastrointestinal tract) cause a difference in pharmacokinetic parameters and, accordingly, in the manifestation of pharmacological effects. Given that these polymorphs are obtained by crystallization from different solvents, it can be assumed that the crystalline structures that are formed are subject to varying degrees to wetting with hydrophilic aqueous medium and the formation of hydrogen connections with the solvent, which precedes their subsequent dissolution. Accordingly, crystalline polymorphic form B, which dissolves more rapidly in the gastrointestinal tract, is absorbed at a higher rate (and degree of absorption) in the intestine and has a pharmacological effect. Toxicological studies (acute lethality and ulcerogenic action) have shown that the safest is the polymorphic modification B, ie crystals in the form of plates [19], which serves as a basis for further in-depth studies of this modification N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide.

Further research in this direction will serve to develop optimal conditions for the development and creation of new biologically active compounds and generic substances to optimize the pharmacodynamic and toxicological parameters of drugs.

Conclusion

1. The results of the study expand the understanding of the role of spatial structure in the manifestations of pharmacological activity and safety of drugs.

2. Based on the analysis of pharmacokinetic parameters of polymorphic forms of N-(4-trifluoromethylphenyl)-4-methyl-2.2-dioxo-1H-2λ6.1-benzothiazine-3-carboxamide, it can be concluded that the polymorphic form in the form of plates (form B), having the largest surface area of the crystal, affects mainly the absorption processes with corresponding changes in the values of absorption, maximum concentration and time of its achievement, has the highest bioavailability and rapid elimination, which correlates with the most optimal pharmacological and toxicological characteristics of this compound compared to other crystalline forms.

3. The results of an in-depth study of the pharmacodynamics and pharmacokinetics of compounds with different crystalline modifications will make it possible to recommend the most active and safe compound for in-depth preclinical study and possible clinical trials as an analgesic and anti-inflammatory agent.

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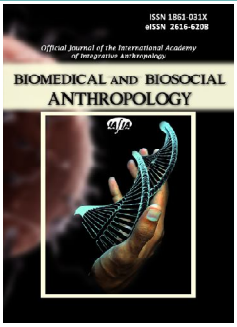

Correlations of basal cranial structures characteristics determined by Bjork and Jarabak methods with teleradiographic parameters of the upper and lower jaws and tooth location in young men and young women with orthognathic occlusion

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The widespread use of methods of cephalometric analysis in practical orthodontics requires the adaptation of normative indicators for members of the local ethnic group. It is also important to study the relationships between cranial and odontometric parameters to understand the effects of these components on each other. The aim of the study was to establish the peculiarities of correlations between the characteristics of basal cranial structures determined by Bjork and Jarabak methods with teleradiographic parameters of the upper and lower jaws and the location of teeth in Ukrainian young men and young women with orthognathic occlusion. Teleradiography was performed in the mode of cephalometric examination of 49 young men (aged 17 to 21 years) and 76 young women (aged 16 to 20 years) who had a physiological bite as close as possible to orthognathic. Cephalometric analysis according to modifications of Jarabak J. R. - Roth-Jarabak and Bjork A. - CFT-Bjork methods, performed using OnyxCeph³™ software, 3DPro version, Image Instruments GmbH, Germany (software license № URSQ-1799). All indicators were divided into three groups according to Dmitriev M. O. (2017): the first group included metric characteristics of the skull, which are used as basic indicators in the methods of cephalometric analysis; to the second group - dental-maxillary in which the skeleton has already been formed and which surgical methods can change the length, width, angles and positions of the upper and lower jaws; to the third group - indicators that actually characterize the position of each individual tooth relative to each other, cranial structures and the profile of the soft tissues of the face. Correlation assessment was performed in the license package "Statistica 6.0" using the non-parametric Spearman method. As a result of the conducted researches in Ukrainian young men and young women with orthognathic occlusion the peculiarities of multiple correlations of characteristics of basal cranial structures determined by CFT-Bjork and Roth-Jarabak methods with teleradiographic parameters of upper and lower jaws and tooth location were established. Both the CFT-Bjork method and the Roth-Jarabak method have more reliable correlations in both young men and young women between the first and second groups (23.3 % for young men and 50.0 % for young women for CFT-Bjork and 48.4 % for young men and 41.1% for young women according to Roth-Jarabak) than between the indicators of the first and third groups (respectively 12.8 % for young men and 7.7 % for young women for CFT-Bjork and 22.5 % for young men and 12.5 % for young women for Roth-Jarabak). The expressed manifestations of sexual dimorphism of the received correlations between the indicators defined by CFT-Bjork and Roth-Jarabak methods both on quantity and force, and in some cases on a direction of correlations are established.

Keywords: *teleradiography, cephalometric analysis by Jarabak and Bjork methods, correlations, Ukrainian young men and young women with orthognathic occlusion.*

Introduction

The rapid development of orthodontics, which takes place both in Ukraine and abroad, is a logical consequence of the rapid spread of anomalies of the dental and maxillofacial system. For example, an analysis of 878

orthopantomograms at the Jeddah Dental Clinic (Saudi Arabia) showed that 45.1 % of patients had at least one dental abnormality. Among the anomalies such pathologies as congenital absence of teeth (25.7 %), retinal detachment (21.1 %) prevailed; curvatures of tooth roots (1.1 %) and excess teeth (0.3 %) were less common [1].

Dental examination of 25,186 Italians found 61 posterior excess teeth in 45 people. The frequency of detection of this phenomenon was higher in men (ratio of men and women 2.5:1). In 62.3 % this pathology was found on the upper jaw [8]. In another study conducted in Italy on a sample of 4006 people, data analysis showed that the prevalence of agenesis was 9 %. The most common was agenesis of the second premolars on the mandible (20.3 % in men and 18.1 % in women). Absence of one to five teeth was observed in 8.6 % of subjects [13].

In Turkey, the prevalence of dental anomalies among children was 2.0 %. As in previous studies, the prevalence of abnormalities was higher in boys than in girls [16]. A survey of 2,469 children in Nitte, India, found that the prevalence of hypodontia was 0.32 % and that of excess teeth was 0.24 %.

In another study conducted in India, the analysis of the obtained data showed that 27.7 % of the subjects had at least one odontological anomaly. Hypodontia, microdontia and hyperdontia were most frequently detected (10.4 %, 7.7 % and 6.3 %, respectively) [29].

Thus, there was a need to find and implement new diagnostic and therapeutic methods. The teleradiographic method of research deserves special attention, which considers cranial and dental-maxillary structures as one complex, which can also affect each other [2]. Numerous methods of analysis have been proposed by leading scientists in the field of odontology for the correct interpretation of the obtained data, each of which has its advantages and disadvantages, therefore the authors often consider several methods in their research combining their indicators [22, 25].

However, the results of studies conducted by domestic researchers have shown that the methods of cephalometric analysis require adaptation for the Ukrainian population considering regional affiliation, gender and age [11, 14, 21, 27].

The aim of the study was to establish the peculiarities of correlations between the characteristics of basal cranial structures determined by Bjork and Jarabak methods with teleradiographic parameters of the upper and lower jaws and the location of teeth in Ukrainian young men and young women with orthognathic occlusion.

Materials and methods

Teleradiography in the mode of cephalometric examination was performed using a dental cone-beam tomograph Veraviewepocs 3D Morita (Japan) for 49 young men (YM) (aged 17 to 21 years) and 76 young women (YW) (aged 16 to 20 years) who had a physiological bite as close as possible to orthognathic (further orthognathic) which is determined by 11 points by Bushan M. G. and others. [6]. Cephalometric analysis according to modifications of the methods Jarabak J. R. [15] - Roth-Jarabak and Bjork A. [5] - CFT-Bjork, performed using OnyxCeph^{3}™ software, 3DPro version, Image Instruments GmbH, Germany (software license № URSQ -1799).

Cephalometric points were determined according to the recommendations of Phulari B. S. [23] and Doroshenko S. I. and Kulginsky E. A. [12].

The main cephalometric points and measurements according to the ***CFT-Bjork*** method:

distance **Ii-Is** (known as Overbite by *CFT-Bjork*) - the distance from the point Is to Ii in the vertical plane, characterizes the inter-cut overlap in the vertical plane (mm);

distance **Ii-NCL** (Lower Lip Protrusion, also known as Li-NsPog' by *Roth-Jarabak*) - the distance from the point Li to the line Ns-Pog`, characterizes the position of the lower lip (mm);

distance **Is-NCL** (also known as: Upper Lip Protrusion and Ls-NsPog' by *Roth-Jarabak*) - the distance from the point Ls to the line Ns-Pog`, characterizes the position of the upper lip (mm);

Is-OIf distance (also known as: Max-Incisor Extrusion 1u-OcP, Max. Incisor to Occl. Plane) - the distance between the point Is and the closing plane (POcp), characterizes the vertical location of the cutting edge of the medial incisor (mm);

Overjet distance (*CFT-Bjork* analysis) - the distance from the point Is to Ii in the sagittal plane, characterizes the inter-cutter distance in the sagittal plane (mm);

Wits distance (*CFT-Bjork* analysis) - the distance between the projections of points A and B on the closing plane (POcp), characterizes the linear ratio of the lower and upper jaws along the folding plane (mm);

angle **A-N-B** (also known as: ss-n-sm, Jaw Relation) - formed by lines A-N and N-B, characterizes the position of the jaws to each other (°);

angle **A-N-Pog** (also known as: ss-n-pg, Jaw Relation to Pog, NAPog, Angle of Convexity) - formed by lines A-N and N-Pog, characterizes the intermaxillary position in the sagittal plane (°);

CL/ML angle (also known as Mandibular alveolar prognathism) - formed by the lines Id-Pog and c-Me, characterizes the position of the mandibular cell sprout (°);

ILi/ML angle (also known as Mandibular incisor inclination) - formed by the central axis of the lower medial incisor and the line tGo-Me, characterizes the position of the lower medial incisor to the plane of the mandible (°);

ILs/ILi angle (also known as: Interincisal Angle according to Roth-Jarabak, inter-incision angle) - formed by the central axes of the upper and lower medial incisors, characterizes the inclination of the upper and lower medial incisors to each other (°);

angle **ILs/NL** (also known as: Max1-SpP Angle, Maxillary incisor inclination) - formed by the central axis of the upper

medial incisor and the line SpP, characterizes the position of the upper medial incisor to the palatal plane (°);

angle **ML/RL** (also known as: Mand. Growth Zone 1, arGoMe, Jaw-/Gonial Angle) - formed by the lines Ar-tGo and tGo-Me, characterizes the angle of the lower jaw (°);

NL/ML angle (also known as: Jaw Relation, Vertical jaw Relationship, SpP-GoMe Angle) - formed by tGo-Me and SpP lines, characterizes the position of the closing plane to the palatal plane (°);

N-S-Ar angle (also known as: Growth Zone 1, NSar Angle, Sella-/Saddle Angle) - formed by N-S and S-Ar lines, characterizes the position of the temporomandibular joint (°);

N-S-Ba angle (also known as: Growth Zone 2, NSBa Angle) - formed by N-S and S-Ba lines, characterizes the angle of the skull base (°);

NSL/ML angle (also known as: Mand. Inclination, SNGoMe Angle, ML-NSL) - formed by lines S-N and tGo-Me, characterizes the inclination of the mandible to the anterior base of the skull (°);

NSL/NL angle (also known as: Max. Inclination, SNSpP Angle, NL-NSL) - formed by S-N and SpP lines, characterizes the inclination of the upper jaw to the anterior base of the skull (°);

angle **OLf/NSL** (also known as: Occl. Plane Inclinatio, SN-OcP Angle) - formed by lines S-N and OcP, characterizes the position of the closing plane to the base of the skull (°);

angle **OLi/ML** (also known as: Mand. Dental Zone, ML/Oli, Mandibular zone, MeGo-OcP Angle) - formed by lines tGo-Me and OcP, characterizes the position of the closing plane to the mandibular plane (°);

angle **OLs/NL** (also known as: Max. Dental Zone, NL/OLs, Maxillary zone, SpP-OcP Angle) - formed by the lines SpP and OcP, characterizes the position of the closing plane to the palatal plane (°);

angle **Pr-N-A** (also known as: pr-n-ss, Maxillary alveolar prognathism) - formed by lines A-N and N-Pr, characterizes the position of the maxillary cell sprout (°);

angle **S-N-A** (also known as: Max. Protrusion, Maxillary prognatism, SNA Angle) - formed by the lines S-N and N-A, characterizes the position of the upper jaw in the sagittal plane (°);

angle **S-N-B** (also known as: Mand. Protrusion, Mandibular alveolar prognathism, SNB Angle) - formed by lines S-N and N-B, characterizes the position of the lower jaw in the sagittal plane (°);

S-N-Pog angle (*CFT-Bjork* analysis - Mand. Protrusion) - is formed by S-N and N-Pog lines, characterizes the position of the lower jaw in the sagittal plane (°);

ratio **N-S:S-Ar'** (Growth Zone 3 N-S) - the ratio of distances N-S and S-Ar', characterizes the position of the projection of the temporomandibular joint on the line N-S (unit).

The main cephalometric points and measurements according to the Roth-Jarabak method:

Ar-Go distance (also known as: Ramus Length, the length of the lower jaw branch) - the distance from the Ar point to the tGo point, which characterizes the length of the lower jaw branch (mm);

distance **Go_Me** (also known as: Body (Mandibular) Length) - the distance from the point tGo to the point Me, characterizes the length of the body of the mandible (mm);

Li-NsPog' distance (also known as: Facial aesthetic line Lower lip, Distance of Lower Lip to Esthetic Line) - the distance from the Li point to the Ns-Pog line, characterizes the position of the lower lip relative to the "Aesthetic line" - the Ns-Pog` line (mm).

distance **Ls-NsPog'** (also known as: Facial aesthetic line upper lip, Distance of Upper Lip to Esthetic Line) - the distance from the point Ls to the line Ns-Pog`, characterizes the position of the upper lip relative to the "Aesthetic line" - the line Ns-Pog` (mm);

N-Go distance (also known as: Facial Depth, depth of the face) - the distance from the point N to the point tGo, characterizes the height of the bony base of the face, and the actual distance of the chin from the point N in the vertical plane (mm);

N-Me distance (also known as: Anterior Facial Height, anterior facial height) - the distance from the N point to the Me point, characterizes the anterior facial height, and the actual distance of the lower chin point Me from the N point (mm);

distance **N-S** (also known as: Anterior Cranial Base Length) - the distance from point N to point S, characterizes the length of the anterior base of the skull (mm);

distance **S-Ar** (also known as: Posterial Cranial Base Length, Length of Lateral Cranial Base, posterior length of skull base, lateral length of skull base) - distance from point S to point Ar, characterizes the location of the temporomandibular joint relative to the Turkish saddle (mm);

distance **S-Gn** (also known as: Facial Length on Y Axis) - the distance from point S to point Gn, characterizes the length of the face determined by the B axis, and the actual distance of the chin from the Turkish saddle (mm);

S-Go distance (also known as: Posterior Facial Height) - the distance from the S point to the tGo point, characterizes the posterior height of the face, and the actual distance of the mandibular angle from the Turkish saddle, also determines the degree of development of the mandibular branch mainly in the vertical plane (mm);

1lo-NPog distance (also known as: Lower incisor to facial plane N-Po, Distance of Incisal Edge of 1l to N-Pog) - the distance from the cutting edge of the lower medial incisor to the N-Pog line, characterizes the anteroposterior position of the lower medial incisor (mm);

1up-NPog distance (also known as: Upper incisor to facial plane N-Po, Distance of Incisal Edge of 1u to N-Pog) - the distance from the cutting edge of the upper medial incisor to the N-Pog line, characterizing the anterior-posterior position of the upper median incisor (mm);

angle **A-N-B** (also known as Angle ANB) - formed by

lines A-N and N-B, characterizes the intermaxillary ratio in the sagittal plane (°);

Ar-Go-Gn angle (also known as: Gonial Angle) - formed by the lines Ar-tGo and tGo-Gn, characterizes the value of the angle of the lower jaw (°);

angle **Il** (also known as: Interincisal Angle) is formed by the central axes of the upper and lower medial incisors, characterizes the angular ratio of the medial incisors of the upper and lower jaws (°);

Mand1-GoMe angle (also known as: Lower incisor to Go-Gn, Angle of Axis of 1l to Mand. Plane) - formed by the central axis of the lower medial incisor and the line tGo-Me, characterizes the inclination of the lower medial incisor to the mandibular plane (°);

angle **Max1-SN** (also known as: 1to Sn, Angle of Axis of 1u to Anterior Cranial Base) - formed by the central axis of the upper medial incisor and the line S-N, characterizes the slope of the upper medial incisor to the anterior base of the skull (°);

N-A-Pog angle (also known as: Facial Convexity (NA-Po), facial convexity angle) - formed by N-A and A-Pog lines, characterizing the convexity of the facial bone profile (°);

N-Go-Ar angle (also known as: Upper Gonial Angle) - formed by the lines N-tGo and tGo-Ar, characterizes the angle of inclination of the lower jaw branch to the line N-tGo (°);

N-Go-Gn angle (also known as: Lower Gonial Angle) - formed by the lines N-tGo and tGo-Gn, characterizes the angle of the mandible to the line N-tGo (°);

N-S-Ar angle (also known as: Saddle Angle) is formed by the N-S and S-Ar lines, characterizes the position of the temporomandibular joint (°);

angle **N-S-Gn** (also known as: Y Axis to SN, angle In the axis) - formed by the lines N-S and S-tGn, characterizes the direction of the axis of development of the mandible (°);

OcP-GoGn angle (also known as: Oclusal plane to G-Gn, Angle of Mand. to Occl. Plane) - is formed by OcP and tGo-Me lines, characterizes the inclination of the closing plane to the mandibular plane (°);

S-Ar-Go angle (also known as: Articular Angle, joint angle) - formed by the lines S-Ar and Ar-tGo, characterizes the position of the temporomandibular joint and the branch of the mandible (°);

angle **S-N-A** (also known as Angle SNA) - formed by the lines S-N and N-A, characterizes the position of the upper jaw in the boom plane (°);

angle **S-N-B** (also known as Angle SNB) - formed by the lines S-N and N-B, characterizes the position of the lower jaw in the boom plane (°);

angle **SN-GoGn** (also known as: Angle of Anterior Cranial Base to Mand. Plane) - formed by the lines SN and tGo-Gn, characterizes the inclination of the lower jaw to the anterior base of the skull (°);

S-N-Pog angle (also known as: Facial Plane (N-Po), face angle) - formed by S-N and N-Pog lines, characterizes the position of the lower jaw, namely the bony chin in the sagittal plane (°);

Sum - the sum of the angles N-S-Ar, S-Ar-Go and Ar-Go-Gn, characterizes the direction of development (vertical when increasing and horizontal when decreasing) of the lower jaw (°);

the ratio of **Go_Me:N-S** - the ratio of the distances Go_Me and N-S, allows you to estimate the degree of development of the lower jaw relative to the anterior base of the skull (%);

the ratio of **S-Ar:Ar-Go** - the ratio of the distances S-Ar and Ar-Go, allows you to assess the degree of development of the branch of the mandible relative to its body (%);

S-Go:N-Me ratio - the ratio of S-Go and N-Me distances, characterizes the ratio between the front and rear face heights (%).

It should be noted that, unlike the original Jarabak analysis, the Roth-Jarabak analysis does not use a specific A-point which is placed 2 mm in front of the apex of the middle maxillary incisor, but uses the more common Downs A-point.

Indicators in this study were divided into three groups according to Dmitriev M. O. [10]. The first group includes metric characteristics of the skull, which are used as basic indicators in the methods of cephalometric analysis; to the second group - dental-maxillary in which the skeleton has already been formed and which surgical methods can change the length, width, angles and positions of the upper and lower jaws; to the third group - indicators that actually characterize the position of each individual tooth relative to each other, cranial structures and the profile of the soft tissues of the face.

Committee on Bioethics of National Pirogov Memorial Medical University, Vinnytsya (Minutes № 8 of 18.10.2019.) It is established that the studies meet the bioethical and moral requirements of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine (1977), the relevant provisions of the WHO and the laws of Ukraine.

Correlation assessment was performed in the license package "Statistica 6.0" using the non-parametric Spearman method.

Results

The results of the evaluation of the correlations between the indicators of the first group by the method of CFT-Bjork or Roth-Jarabak with the indicators of the second and third groups are presented in tables 1 and 2.

Discussion

Manifestations of sexual dimorphism were detected in the study of teleradiograms by the Bjork-Jarabak method of 100 people living in Bangladesh. According to the analysis of the data, men have in comparison with women the values of the saddle angle, gonial angle, body length of the lower jaw, incisor angle and anterior height of the face. In general, it was also found that the indicators for both

Table 1. Correlations of the first group of indicators according to the CFT-Bjork method (names of indicators without color selection) with the second (names of indicators are highlighted in light gray) and the third (names of indicators are highlighted in dark gray) groups.

Indexes	Young men			Young women		
	N-S-Ar	N-S-Ba	N-S:S-Ar'	N-S-Ar	N-S-Ba	N-S:S-Ar'
S-N-A	-0.27	-0.25	0.19	**-0.44**	**-0.36**	**0.38**
S-N-Pog	**-0.43**	**-0.39**	**0.32**	**-0.43**	**-0.40**	**0.33**
S-N-B	**-0.43**	**-0.38**	**0.35**	**-0.40**	**-0.36**	**0.30**
A-N-Pog	0.24	0.17	-0.20	-0.02	0.05	0.04
A-N-B	0.26	0.20	-0.24	-0.11	-0.06	0.12
NSL/NL	0.25	0.18	-0.01	**0.42**	**0.37**	**-0.34**
NSL/ML	**0.29**	0.26	-0.23	**0.39**	**0.39**	**-0.33**
NL/ML	0.21	0.23	-0.27	0.10	0.13	-0.13
li-ls	0.12	0.01	-0.14	-0.14	-0.08	0.14
ML/RL	-0.06	-0.06	-0.02	0.18	0.17	-0.19
Pr-N-A	0.11	0.16	-0.11	-0.02	-0.02	0.01
CL/ML	0.14	0.12	-0.08	0.00	0.03	0.01
ILs/NL	-0.21	-0.11	0.24	0.13	0.13	-0.13
ILi/ML	0.17	0.15	-0.17	-0.11	-0.13	0.18
ILs/ILi	-0.08	-0.11	0.15	0.00	-0.01	-0.03
Overjet	0.11	0.16	-0.13	-0.11	-0.08	0.14
Wits	0.20	0.11	-0.21	-0.15	-0.12	0.15
OLs/NL	**0.33**	**0.30**	**-0.35**	0.06	0.07	-0.08
OLi/ML	-0.04	-0.05	-0.06	0.06	0.12	-0.10
OLf/NSL	**0.35**	**0.35**	-0.26	**0.45**	**0.42**	**-0.41**
ls-OLf	0.23	0.14	-0.07	-0.06	-0.01	0.08
ls-NCL	0.19	0.21	-0.08	-0.10	-0.05	0.19
li-NCL	0.10	0.14	-0.03	-0.01	0.06	0.08

Notes: here and in the following table, significant direct weak correlations are highlighted in yellow; red color accurate direct medium strength correlation; the significant inverse mean correlations are highlighted in blue.

men and women differed significantly from the normative indicators for Bjork-Jarabak [3].

Differences in cephalometric parameters according to Bjork-Jarabak were found for the population of Saudi Arabia. Thus, the largest differences were found for the length of the anterior and posterior part of the face, the height of the branch and the length of the mandible, the length of the anterior and posterior cranial part [4].

Jarabak cephalometric standards have been established for Pakistanis. Differences with the control sample were found for such indicators as upper and lower gonial angle, saddle angle ($p<0.001$), anterior facial height, posterior facial height, anterior and posterior skull base ($p<0.05$) [17].

In another study conducted on a Pakistani sample of individuals, however, using Bjork-Jarabak analyzes, the authors found no differences among virtually all indicators except joint angle and PFH/AFH ratio [20].

Features of cephalometric indicators according to Jarabak are established for the population of Nepal. Statistically significant differences were found for 10 of the 30 studied indicators. In addition, manifestations of sexual dimorphism were detected for 11 of the 30 studied parameters [24].

Processing of cephalometric analysis data by Bjork 122 Polish adolescents revealed the relationship between odontometric parameters and indicators of facial soft tissues [19].

P. Vasanthan and others [28] estimated the height of teeth in malocclusions using cephalometric analysis by Bjork. To conduct this work, the authors analyzed the indicators before and after treatment. Statistically significant results were obtained for the height of the teeth of the mandible measured from the plane of the mandible and the plane CSm.

Interdependencies between cranial structures and odontometric parameters using cephalometric analysis by Downs, Steinner, Bjork, Ricketts and McNamara were found when working with the Brazilian population sample [7, 18].

A correlation between Bjork growth rates and skeletal model prediction was found by Davidovitch M. and co-authors [9]. It was found that only LAFH correlated with age in all study groups.

In the analysis of multiple correlations of the *first group* of indicators according to the *CFT-Bjork method* (values of **N-S-Ar** and **N-S-Ba** angles and the ratio **N-S:S-Ar'**) with the *second group* of indicators in both YM and YW, reliable mean inverse values were established of the magnitude of the angles **N-S-Ar** and **N-S-Ba** (r = from -0.38 to -0.43 in YM and r = from -0.36 to -0.43 in YW) and reliable medium-strength direct correlations of the ratio **N-S:S-Ar'** (r = 0.32 and 0.35 in YM and r = 0.30 and 0.33 in YW) with the value of the angles **S-N-Pog** and **S-N-B**; and only in *YW* - reliable medium-strength feedback of the magnitude of the angles **N-S-Ar** and **N-S-Ba** (r = -0.36 and -0.44) and reliable average-strength direct correlations of the ratio **N-S:S-Ar'** (r = 0.38) with the value of the angle **S-N-A**, as well as reliable average strength direct correlations of the values of the angles **N-S-Ar** and **N-S-Ba** (r = from 0.37 to 0.42) and reliable average strength feedback of the ratio **N-S:S-Ar'** (r = - 0.33 and -0.34) with the value of the angles **NSL/NL** and **NSL/ML**.

In the analysis of multiple correlations of the *first group* of indicators by the *CFT-Bjork method* with the *third group* of indicators in *YM*, only reliable medium-strength direct correlations between the magnitude of the angles **N-S-Ar** and **N-S-Ba** (r = from 0.30 to 0.35) with the magnitude of the angles **OLs/NL** and **OLf/NSL**, as well as a significant average feedback of the ratio **N-S:S-Ar'** (r = -0.35) with the value of the angle **OLs/NL**; and in *YW* - only reliable medium-strength direct correlations of the magnitude of the angles **N-S-Ar** and **N-S-Ba** (r = 0.42 and 0.45), as well

Table 2. Correlations of the first group of indicators according to the Roth-Jarabak method (names of indicators without color selection) with the second (names of indicators are highlighted in light gray) and the third (names of indicators are highlighted in dark gray) groups.

Indexes	Young men					Young women				
	N-S-Ar	N-S	S-Ar	Ar-Go	S-Ar:Ar-Go	N-S-Ar	N-S	S-Ar	Ar-Go	S-Ar:Ar-Go
S-Ar-Go	-0.60	-0.07	-0.06	-0.35	0.22	-0.69	0.19	0.08	-0.04	0.06
Ar-Go-Gn	-0.06	-0.32	0.04	-0.50	0.42	0.19	-0.09	-0.14	-0.42	0.19
Sum	0.27	-0.48	-0.23	-0.65	0.37	0.41	-0.17	-0.31	-0.47	0.12
N-Go-Ar	-0.02	0.28	0.27	-0.04	0.16	0.09	0.12	0.06	-0.33	0.26
N-Go-Gn	-0.04	-0.59	-0.07	-0.61	0.43	0.16	-0.21	-0.19	-0.32	0.10
Go_Me	0.19	0.51	0.09	0.41	-0.29	0.02	0.40	0.36	0.34	0.03
Go_Me:N-S	0.30	0.02	-0.04	0.29	-0.24	0.26	-0.32	0.09	0.19	-0.06
S-N-A	-0.27	0.20	0.16	0.51	-0.30	-0.44	-0.13	0.08	0.10	-0.05
S-N-B	-0.43	0.25	0.13	0.53	-0.35	-0.40	-0.10	0.11	0.21	-0.12
A-N-B	0.22	-0.10	-0.05	-0.07	0.06	-0.09	-0.08	-0.03	-0.10	0.05
SN-GoGn	0.27	-0.48	-0.23	-0.65	0.37	0.41	-0.17	-0.31	-0.47	0.12
N-Go	0.30	0.46	0.35	0.47	-0.16	-0.01	0.56	0.46	0.59	-0.06
S-Gn	-0.11	0.28	0.38	0.24	-0.01	-0.25	0.56	0.42	0.36	0.05
N-S-Gn	0.40	-0.50	-0.12	-0.49	0.35	0.50	-0.23	-0.14	-0.20	0.08
S-Go	-0.13	0.29	0.48	0.71	-0.23	-0.35	0.36	0.56	0.74	-0.10
N-Me	0.24	-0.04	0.26	-0.11	0.24	0.11	0.41	0.29	0.24	0.06
S-Go:N-Me	-0.31	0.36	0.29	0.66	-0.33	-0.42	0.11	0.41	0.54	-0.09
S-N-Pog	-0.44	0.32	0.22	0.50	-0.29	-0.41	-0.04	0.16	0.26	-0.11
N-A-Pog	0.21	-0.15	-0.13	-0.08	0.04	0.00	-0.16	-0.12	-0.16	0.02
OcP-GoGn	-0.03	-0.29	0.02	-0.52	0.35	0.12	-0.11	-0.17	-0.29	0.10
Il	-0.08	-0.17	-0.08	-0.33	0.22	0.00	-0.03	-0.04	0.15	-0.15
Max1-SN	-0.25	0.27	0.15	0.47	-0.31	-0.14	0.01	0.13	0.08	0.03
Mand1-GoMe	0.17	0.31	0.06	0.48	-0.33	-0.11	0.18	0.12	0.13	0.00
1up-NPog	0.24	-0.10	-0.14	0.12	-0.14	0.02	-0.11	-0.06	-0.27	0.13
1lo-NPog	0.19	-0.20	-0.17	0.04	-0.10	0.07	-0.12	-0.14	-0.24	0.06
Ls-NsPog'	0.18	0.05	-0.14	0.03	-0.06	-0.11	-0.11	-0.18	-0.23	0.02
Li-NsPog'	0.07	-0.09	-0.20	0.02	-0.08	-0.01	-0.11	-0.11	-0.33	0.13

Notes: significant direct strong correlations are highlighted in magenta; significant inverse weak correlation forces are highlighted in green; significant inverse strong correlations are highlighted in purple.

as reliable average-strength feedback of the ratio **N-S:S-Ar'** (r = -0.41) with the value of the angle **OLf/NSL**.

Our *quantitative analysis of significant correlations* in Ukrainian YM and YW with orthognathic occlusion between the characteristics of the basal cranial structures (first group) by *CFT-Bjork* with teleradiographic parameters of the upper and lower jaws (second group) and the location of teeth (third group) revealed the following distribution correlations:

with indicators of the second group - YM have 7 correlations out of 30 possible (23.3 %), of which, 6.7 % of direct medium strength and 3.3 % of direct weak force and 13.3 % of reverse medium force; YW have 15 correlations out of 30 possible (50.0 %), of which 23.3% are direct medium strength and 26.7 % are reverse medium strength;

with indicators of the third group - YM have 5 correlations out of 39 possible (12.8 %), of which, 10.3% are direct medium strength and 2.6 % are reverse medium strength; YW have 3 correlations out of 39 possible (7.7 %), of which 5.1 % are direct medium strength and 2.6 % reverse medium strength.

In the analysis of multiple correlations of the *first group* of indicators by the *Roth-Jarabak method* (the value of the angle **N-S-Ar**, the distances **N-S**, **S-Ar** and **Ar-Go** and the ratio **S-Ar:Ar-Go**) with the second group of indicators in *YM* found reliable, mostly average forces, direct and feedback correlations of values of **Ar-Go** distances (r = from 0.29 to 0.71 and r = from -0.35 to -0.65) and N-S (r = from 0.28 to

0.51 and r = from -0.32 to -0.59) and the ratio of **S-Ar:Ar-Go** (r = from 0.35 to 0.43 and r = from -0.29 to -0.35) with most indicators of the second group, also only direct, mostly medium-strength (r = from 0.29 to 0.48) correlations of distances **S-Ar** with the value of distances **N-Go**, **S-Gn** and **S-Go** and the ratio **S-Go:N-Me**; and in *YW* - reliable, mostly of medium strength inverse, correlations (r = from -0.25 to -0.69) of the value of the angle **N-S-Ar** with almost half of the indicators of the second group, as well as reliable, mostly of medium strength direct, correlations of distances **S-Ar** (r = from 0.29 to 0.56) and **N-S** (r = from 0.36 to 0.56) with almost half of the indicators of the second group and reliable, mostly medium-strength, direct and feedback correlations of **Ar-Go** distances (r = from 0.24 to 0.74 and r = from -0.32 to -0.47) with most indicators of the second group.

In the analysis of multiple correlations of the *first group* of indicators according to the *Roth-Jarabak method* with the third group of indicators in *YM*, only reliable average strength direct (r = 0.47 and 0.48) and average strength inverse (r = -0.33 and -0.52) correlations of the distance **Ar-Go** with the magnitude of the angles **Max1-SN** and **Mand1-GoMe** (straight) and the magnitude of the angles **OcP-GoGn** and II (reverse) and vice versa, the significant mean strength of the inverse (r = -0.31 and -0.33) and the average strength direct (r = 0.35) correlation of the ratio **S-Ar:Ar-Go** with the magnitude of the angles **Max1-SN** and **Mand1-GoMe** (reverse) and the magnitude of the angle **OcP-GoGn** (direct); and in *YW* - only reliable, mostly weak force, inverse (r = from -0.23 to -0.33) correlations of the value of the distance **Ar-Go** with the value of the angle **OcP-GoGn** and the value of the distances **1up-NPog**, **1lo-NPog**, **Ls-NsPog'** and **Li-NsPog'**.

Our *quantitative analysis of significant correlations* in Ukrainian YM and YW with orthognathic occlusion between the indicators of the characteristics of basal cranial structures (first group) by *Roth-Jarabak* method with teleradiographic parameters of the upper and lower jaws (second group) and the location of teeth (third group) revealed the following distribution correlations:

with indicators of the second group - in YM 46 correlations from 95 possible (48.4 %), from which, 2.1 % of direct strong, 21.1 % of direct average force and 4.2 % of direct weak force and 4.2 % of return strong, 14.7 % of return of average force and 2.1 % of weak force reversals; *YW* have 39 correlations out of 95 possible (41.1 %), of which, 1.1 % direct strong, 17.9 % direct medium strength and 5.3 % direct weak force and 1.1 % reverse strong, 13.7 % reverse medium strength and 2.1 % reverse weak force ;

with indicators of the third group - in YM 9 correlations out of 40 possible (22.5 %), of which, 10.0 % of direct medium strength, 10.0 % of reverse of medium strength and 2.5 % of reverse of weak strength; *YW* have only 5 correlations out of 40 possible (12.5 %), of which, 10.0 % are weak-strength and 2.5 % are moderate-strength.

Thus, the established features of correlations of characteristics of basal cranial structures determined by CFT-Bjork and Roth-Jarabak methods with teleradiographic parameters of the upper and lower jaws and the location of teeth in Ukrainian YM and YW with orthognathic occlusion will allow more reasonable and correct interpretation of the data. teleradiograms by these methods.

Conclusion

1. In Ukrainian YM and YW with orthognathic occlusion, qualitative and quantitative features of correlations of characteristics of basal cranial structures determined by CFT-Bjork and Roth-Jarabak methods with teleradiographic parameters of upper and lower jaws and tooth location were established.

2. Manifestations of sexual dimorphism of correlations between the indicators determined by the methods of CFT-Bjork and Roth-Jarabak both in number and strength, and in the direction of correlations was established.

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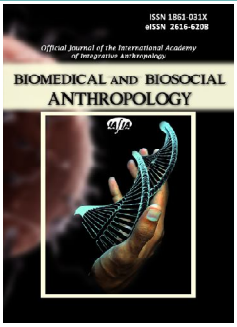

Correlations between the severity of oily skin and the emotional impact of oily skin with anthropo-somatotypological parameters of men and women with seborrheic dermatitis

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The increase in the prevalence and age of seborrhea, its significant impact on the psycho-emotional sphere, social status and social adaptation of patients determines the relevance of further study of the causes of dermatosis in the key of constitutional psychodermatology, namely - the study of relationships between oily skin and emotional impact of oily skin with anthropometric indicators. The aim of the study was to analyze the correlations between Oily Skin Self Assessment Scale (OSSAS) and Oily Skin Impact Scale (OSIS) in men and women with seborrheic dermatitis with body structure and size indicators. A survey of 40 men and 40 young women with generalized fatty seborrheic dermatitis done. The OSSAS and OSIS scoring system was used to assess the severity of oily skin and the emotional impact of oily skin in seborrheic dermatitis. Anthropometric survey was carried out according to the scheme of Bunak V. V. (1941). The mathematical scheme of Carter J. and Heath B. (1990) was used to evaluate the somatotype. Matiegka J. (1921) formulas were used to calculate body weight components. In addition, the muscle component of body weight was assessed by the American Nutrition Institute. Correlation analysis was performed in the license package "Statistica 6.0" using the non-parametric Spearman's method. As a result of the conducted researches multiple reliable and moderate unreliable correlations of OSSAS or OSIS with anthropo-somatotypological indicators of men and women of patients with generalized fatty form of seborrheic dermatitis of mild and severe course were established. The practical lack of similar correlations between OSIS and anthropo-somatotypological parameters in men and women with severe seborrheic dermatitis is noteworthy. Quantitative analysis of reliable and moderate unreliable correlations of OSSAS or OSIS with anthropo-somatotypological parameters in men and women with seborrheic dermatitis of mild and severe course showed that the vast majority of such correlations are inverse, and unreliable average correlations are often observed (except for OSSAS correlations with anthropo-somatotypological parameters in women with mild disease). It was also found that regardless of sex, most of the reliable or moderately unreliable correlations between OSSAS or OSIS and anthropo-somatotypological indicators are observed in the mild course of the disease. The obtained results of the correlation analysis expand the current understanding of the risk criteria and unfavorable prognosis of seborrheic dermatitis.

Keywords: *seborrheic dermatitis, Oily Skin Self Assessment Scale (OSSAS), Oily Skin Impact Scale (OSIS), anthropometric indicators, somatotypological indicators, correlations.*

Introduction

The activity of the sebaceous glands depends on many components and the amount of sebum can change throughout life. Oily skin is most common in young people during puberty, but is often associated with the constitutional type. Hypertensives are more likely to have thick and oily skin. It is thick, covered with large pores filled with sebaceous glands, comedones, prone to acne, has a greasy sheen, often gray. The test for fat in the central and lateral parts of the face is positive [17].

In itself, increased oiliness of the skin is not dangerous

for humans, but causes some discomfort - both physiological and psychological [8]. In comparison with healthy individuals with high oiliness of the skin in patients with seborrhea, there is an increase in the composition of sebum androgens and a decrease in estrogen. With seborrhea in the sebum decreases the concentration of linoleic acid, which leads to an increase in skin pH, changes in epithelial permeability, an increase in the number of microorganisms on the skin surface. The main manifestations of the disease - itching, peeling, the appearance of white scales-crusts, redness and swelling of the affected areas [5, 7, 11].

According to studies by foreign colleagues [6, 8], patients with increased oiliness significantly reduce the quality of life, increase the frequency of anxiety and depression, subjective discomfort compared to healthy peers. In our domestic sample, similar indicators of psycho-emotional state due to the degree of oiliness of the skin have not been studied so far. Increasing the prevalence and expansion of the age limits of this pathology, its significant impact on the psycho-emotional sphere, social status and social adaptation of patients determines the urgency of this problem and the need for further study of the causes of seborrhea in the context of constitutional psychodermatology.

The purpose of the study - to analyze the correlations between the severity of oily skin (OSSAS) and the emotional impact of oily skin (OSIS) in men and women with seborrheic dermatitis with indicators of body structure and size.

Materials and methods

Survey of 40 men and 40 young women (25-44 years according to the age periodization of the WHO, 2015) patients with generalized fatty seborrheic dermatitis was conducted on the basis of the Department of Skin and Venereal Diseases with a postgraduate course in National Pirogov Memorial Medical University, Vinnytsya and the Military Medical Clinical Center of the Central Region.

The OSSAS scoring system was used to assess the severity of oily skin in seborrheic dermatitis [1]. The intensity of the main symptoms of oily skin is assessed on a 5-point scale: 1 - not very; 2 - soft; 3 - moderately; 4 - strongly; 5 - very strong. Final evaluation of indicators: 12-36 points - easy course; 37-60 points - severe course.

The OSIS scoring system was used to assess the severity of the emotional impact of oily skin [1]. The influence of oily skin on the emotional state of the body is assessed on a 5-point scale: 1 - does not bother; 2 - to put it mildly, worries; 3 - moderately disturbing; 4 - much disturbing; 5 - very disturbing. Final evaluation of indicators: 2-6 points - mild course; 6-10 points - severe course.

Anthropometric survey was conducted according to the scheme of Bunak V. V. [3]. The mathematical scheme of Carter J. and Heath B. was used to evaluate the somatotype [4]. J. Matiegka's formulas were used to calculate fat, bone and muscle components of body weight [13]. In addition, the muscle component of body weight was assessed by the method of the American Institute of Nutrition (AIN) [16].

Correlation analysis was performed in the license package "Statistica 6.0" using the non-parametric Spearman's method.

Results

Correlations between the severity of oily skin (OSSAS) or the severity of the emotional impact of oily skin (OSIS) with the structure and size of men and women with seborrheic dermatitis of mild and severe course are shown in tables 1 and 2.

Table 1. Correlations of OSSAS with indicators of body structure and size of men and women with seborrheic dermatitis of mild and severe course.

Indexes	Men		Women	
	mild course	severe course	mild course	severe course
OB_GL	-0.20	**-0.45**	***-0.36***	-0.01
SAG_DUG	***-0.39***	-0.19	-0.13	-0.13
B_DL_GL	***-0.31***	-0.09	0.11	0.20
B_SH_GL	0.18	***-0.40***	-0.14	0.03
N_SH_GL	-0.18	***-0.39***	0.07	-0.15
SH_LICA	-0.04	0.06	-0.28	0.02
SH_N_CH	0.04	0.02	-0.09	***0.40***
W	-0.24	***-0.30***	**-0.51**	***-0.41***
H	-0.13	0.00	***-0.38***	***-0.41***
S	-0.22	-0.25	***-0.31***	***-0.43***
ATND	-0.19	0.09	***-0.36***	***-0.42***
ATL	0.01	0.20	***-0.33***	-0.24
ATPL	-0.17	0.14	***-0.38***	**-0.46**
ATP	-0.21	-0.28	-0.27	-0.21
ATV	0.09	0.18	-0.29	-0.27
EPPL	***-0.30***	-0.21	***-0.31***	***-0.32***
EPPR	-0.08	-0.12	**-0.55**	***-0.41***
EPB	-0.14	**-0.50**	**-0.51**	-0.17
EPG	-0.15	**-0.60**	**-0.54**	**-0.44**
OBPL1	***-0.40***	***-0.35***	**-0.56**	***-0.32***
OBPL2	**-0.49**	-0.20	***-0.36***	-0.21
OBPR1	**-0.53**	-0.26	-0.28	***-0.30***
OBPR2	-0.11	***-0.44***	**-0.48**	-0.23
OBB	-0.14	-0.10	**-0.53**	-0.29
OBG1	***-0.32***	-0.26	**-0.60**	-0.20
OBG2	-0.29	-0.25	***-0.40***	-0.11
OBSH	0.02	-0.18	**-0.45**	-0.06
OBT	***-0.40***	-0.23	**-0.31**	***-0.32***
OBBB	-0.01	***-0.36***	**-0.48**	***-0.38***
OBK	-0.15	-0.28	***-0.40***	***-0.30***
OBS	***0.31***	-0.09	**-0.57**	-0.06

Continuation of table 1.

Indexes	Men		Women	
	mild course	severe course	mild course	severe course
OBGK1	***-0.34***	-0.28	-0.29	-0.23
OBGK2	***-0.39***	***-0.31***	***-0.31***	***-0.42***
OBGK3	***-0.35***	-0.24	-0.26	***-0.35***
PSG	-0.23	***-0.32***	***-0.30***	-0.18
PNG	***-0.40***	-0.14	-0.14	-0.12
SGK	**-0.55**	-0.06	**-0.55**	**-0.45**
ACR	0.04	-0.03	**-0.58**	-0.10
SPIN	-0.16	-0.14	***-0.44***	0.01
CRIS	-0.17	-0.21	**-0.50**	-0.03
TROCH	0.04	**-0.49**	**-0.51**	-0.21
CONJ			**-0.61**	-0.29
GZPL	0.09	0.08	***-0.33***	-0.09
GPPL	0.20	-0.08	***-0.30***	***-0.40***
GPR	0.27	0.11	**-0.50**	-0.29
GL	-0.27	-0.24	**-0.49**	***-0.37***
GGR	**0.64**	0.20	***-0.33***	0.26
GG	-0.28	-0.17	***-0.40***	-0.26
GB	***-0.30***	-0.08	**-0.50**	***-0.31***
GBD	-0.27	0.13	**-0.45**	-0.18
GGL	-0.22	-0.19	-0.16	-0.23
FX	***-0.31***	-0.15	**-0.50**	***-0.30***
MX	***-0.30***	***-0.32***	**-0.52**	-0.18
LX	0.18	***0.30***	**0.51**	0.26
SOMAT	***0.38***	***0.38***	0.24	0.16
MM	***-0.35***	-0.25	***-0.31***	***-0.39***
OM	-0.29	**-0.50**	**-0.52**	***-0.40***
DM	-0.28	-0.25	***-0.37***	***-0.33***
MA	**-0.46**	-0.15	***-0.30***	-0.27

Notes: here and in the following table, inaccurate direct correlations of medium strength are highlighted in yellow; reliable direct correlations of medium strength are highlighted in magenta; strong reliable direct correlations are highlighted in red; inaccurate inverse correlations are highlighted in green; significant inverse correlations of medium strength are highlighted in blue; strong reliable inverse correlations are highlighted in purple; OB_GL - head circumference (cm); B_DL_GL - the largest length of the head (cm); N_SH_GL - the smallest width of the head (cm); SH_N_CH - width of the lower jaw (cm); SAG_DUG - sagittal arch of the head (cm); B_SH_GL - the largest width of the head (cm); SH_LICA - face width (cm); W - body weight (kg); H - body length (cm); ATND - height of the upper thoracic point (cm); ATL - pubic point height (cm); ATPL - height of the acromial point (cm); ATP - height of the finger point (cm); ATV - height of the trochanteric point (cm); EPPL - width of the distal epiphysis (WDE) of the shoulder (cm); EPPR - WDE forearm (cm); EPB - WDE thigh (cm); EPG - WDE of shin (cm); OBPL1 - shoulder girth in a tense state (cm); OBPL2 - shoulder girth in the unstressed state (cm); OBPR1 - forearm girth in the upper part (cm); OBPR2 - forearm girth in the lower part (cm); OBB - hip girth (cm); OBG1 - shin girth in the upper part (cm); OBG2 - shin girth in the lower part (cm); OBSH - neck circumference (cm); OBT - waist circumference (cm); OBBB - hip circumference (cm); OBK - girth of the hand (cm); OBS - foot circumference (cm); OBGK1 - chest girth on inspiration (cm); OBGK2 - chest girth on exhalation (cm); OBGK3 - chest girth with calm breathing (cm); PSG - transverse mid-chest size (cm); PNG - transverse lower chest size (cm); SGK - anterior-posterior size of the chest (cm); ACR - shoulder width (cm); SPIN - interspinous distance (cm); CRIS - intercristal distance of the pelvis (cm); TROCH - intertrochanteric distance of the pelvis (cm); CONJ - superficial conjugate (cm); GZPL - thickness of skin and fat folds (TSFF) on a back surface of a shoulder (mm); GPPL - TSFF on a front surface of a shoulder (mm); GPR - TSFF on a forearm (mm); GL - TSFF at the lower angle of the scapula (mm); GGR - TSFF on a breast (mm); GG - TSFF on the abdomen (mm); GB - TSFF on the side (mm); GBD - TSFF on a hip (mm); GGL - TSFF on crus (mm); FX - endomorphic component of the somatotype (scores); MX - mesomorphic component of the somatotype (scores); LX - ectomorphic component of the somatotype (scores); SOMAT - type of somatotype (1 - endomorphs, 2 - mesomorphs, 3 - ectomorphs, 4 - ectomesomorphs, 5 - endomesomorphs, 6 - middle intermediate); MM - muscle component of body weight according to Matiegka (kg); OM - bone component of body weight according to Matiegka (kg); DM - fat component of body weight according to Matiegka (kg); MA - muscle component of body weight by the method of AIN (kg).

Table 2. Correlations of OSIS with indicators of body structure and sizes of men and women with mild and severe seborrheic dermatitis.

Indexes	Men		Women	
	mild course	severe course	mild course	severe course
OB_GL	**-0.56**	-0.12	***0.35***	***-0.33***
SAG_DUG	0.20	-0.04	**0.46**	-0.24
B_DL_GL	0.02	-0.25	**0.77**	-0.12
B_SH_GL	***-0.33***	-0.19	0.09	0.06
N_SH_GL	**-0.56**	0.00	0.17	0.00
SH_LICA	-0.20	0.23	***0.32***	0.17
SH_N_CH	***-0.32***	0.23	***0.35***	0.12
W	-0.28	-0.01	-0.20	0.01
H	0.28	-0.06	0.16	-0.15
S	-0.11	-0.01	-0.01	-0.01
ATND	0.18	-0.11	0.12	-0.24
ATL	0.07	-0.27	-0.13	***-0.34***
ATPL	0.18	-0.12	0.17	-0.21
ATP	***-0.36***	***-0.36***	***0.39***	-0.29
ATV	0.00	-0.26	-0.05	***-0.36***
EPPL	***-0.30***	0.02	-0.24	-0.02
EPPR	0.12	0.11	-0.25	-0.14
EPB	***-0.31***	-0.04	0.12	-0.06
EPG	0.09	-0.21	0.05	-0.18
OBPL1	-0.17	-0.09	-0.14	0.03
OBPL2	-0.20	-0.09	***-0.31***	0.03
OBPR1	***-0.33***	0.02	-0.19	-0.10
OBPR2	-0.02	0.02	-0.28	-0.04
OBB	***-0.42***	-0.01	-0.25	-0.12
OBG1	-0.28	0.08	0.00	-0.25

Continuation of table 2.

Indexes	Men		Women	
	mild course	severe course	mild course	severe course
OBG2	-0.15	-0.10	0.05	-0.16
OBSH	***-0.38***	0.16	**-0.62**	-0.11
OBT	**-0.56**	0.16	**-0.49**	-0.08
OBBB	-0.28	0.14	***-0.39***	-0.05
OBK	0.01	***0.30***	-0.21	0.07
OBS	-0.02	-0.02	-0.11	-0.25
OBGK1	**-0.45**	-0.08	**-0.53**	0.00
OBGK2	***-0.37***	0.04	***-0.40***	0.09
OBGK3	**-0.47**	-0.04	**-0.52**	0.00
PSG	***-0.38***	-0.01	-0.24	0.17
PNG	***-0.39***	0.00	***-0.32***	0.16
SGK	-0.21	0.02	***-0.35***	-0.04
ACR	**-0.49**	0.00	**-0.56**	-0.01
SPIN	-0.17	***0.31***	-0.11	-0.07
CRIS	-0.15	***0.33***	-0.18	-0.09
TROCH	-0.18	0.10	-0.06	-0.01
CONJ			-0.26	-0.10
GZPL	-0.12	-0.03	***-0.33***	0.03
GPPL	***-0.30***	0.09	-0.27	0.03
GPR	-0.01	0.01	-0.05	0.01
GL	***-0.43***	0.13	-0.01	0.02
GGR	-0.17	-0.08	**-0.54**	***0.34***
GG	***-0.43***	0.24	***-0.31***	0.21
GB	***-0.38***	0.26	-0.11	0.18
GBD	-0.28	-0.01	-0.28	***0.39***
GGL	-0.26	0.09	0.11	0.17
FX	***-0.41***	0.22	-0.06	0.10
MX	**-0.48**	0.04	***-0.30***	-0.07
LX	***0.37***	-0.09	***0.39***	0.05
SOMAT	0.26	-0.04	***0.36***	0.19
MM	***-0.39***	-0.01	-0.07	-0.15
OM	-0.11	-0.09	0.07	-0.11
DM	***-0.36***	0.10	-0.16	0.15
MA	-0.03	-0.11	***-0.31***	-0.01

Discussion

Possible causes of seborrhea - hereditary predisposition, the influence of external adverse factors, metabolic disorders and neuroendocrine disorders. The disease affects people of different ages and social status [2, 18, 19].

Anthropological approach in the clinic of skin diseases allows you to correctly and timely diagnose the problem, identify risk groups and build a whole prognostic system for a particular dermatosis [9, 10, 12, 14]. The literature provides data on the constitutional and hereditary nature of the predisposition to seborrhea, which are generalized by polygenic or multifactorial type of inheritance. There is scientific evidence of the influence of constitutional factors on the possible development of dermatosis, including weight, height and body mass index. The composition of sebum in people of different constitutional types differs significantly and varies with varying degrees of pathological condition [15, 20]. Despite the fact that in the screening diagnosis of seborrhea the traditional place is occupied by information obtained using dermatological and general clinical methods of examination, no less important in the diagnosis of dermatosis are data that take into account somatotype and its relationship to skin oiliness and emotional state of patient.

The analysis of *OSSAS* correlations with *anthropo-somatotypological* indicators of men and women with mild and severe seborrheic dermatitis revealed the following multiple reliable and moderate unreliable correlations:

in men with a mild course of the disease - moderate reverse (r = from -0.31 to -0.53), mostly unreliable, correlations with more than half of the girth body sizes and as a consequence with the mesomorphic component of the somatotype (r = -0.30) and muscular components of body weight according to Matiegka and AIN (r = -0.35 and -0.46);

in men with severe disease course - attract attention only reliable medium strength and strong feedback from WDE of long tubular bones of the lower extremities (r = -0.50 and -0.60);

in women with a mild course of the disease - moderate inverse (r = from -0.30 to -0.52), mostly unreliable, correlations with all total, most longitudinal body size and all indicators of the component composition of body weight; medium strength inverse (r = from -0.31 to -0.55), mostly reliable, connections with all indicators of WDE of long tubular bones of extremities; inverse, mostly moderate (r = -0.30 to -0.61), reliable and unreliable correlations with most of the girth, transverse body size and indicators of TSFF; medium strength significant inverse (r = -0.50 and -0.52) correlations with endo- and mesomorphic components of the somatotype and medium strength reliable direct (r = 0.51) correlations with the ectomorphic component of the somatotype;

in women with severe disease course - moderate reversible (r = from -0.30 to -0.44), mostly unreliable, correlations with all total, most indicators of WDE of long tubular bones of the extremities and indicators of the component composition of body weight, almost half the girth body sizes and a third of TSFF indicators.

A *quantitative analysis of reliable and moderate unreliable correlations* in men and women with mild to severe seborrheic dermatitis between OSSAS and anthropo-somatotypological indicators revealed the following distribution of correlations:

in men with a mild course of the disease - 21 correlations out of 58 possible (36.2 %), among which 1.7 % of strong direct reliable, 1.7 % of average force of unreliable, 6.9 % of

average force of reverse reliable and 25.9 % of average force of reverse unreliable. The relative majority of correlations were established with somatotype components (66.7 % - all mean inverse inaccuracies), girth body sizes (13.3 % of mean inverse force and 46.7 % of mean inverse inaccuracy), transverse torso sizes and indicators of the component composition of body weight (by 25.0 % of the average strength of the inverse reliable and 25.0 % of the average strength of the inverse unreliable);

in men with a severe course of the disease - 16 correlations out of 58 possible (27.6 %), among which 3.4 % of the average force of direct unreliable, 1.7 % of strong inverse reliable, 6.9 % of the average force of inverse reliable and 15.5 % of the average force of inverse unreliable. The relative majority of correlations are established with components of a somatotype (by 33.3 % of average force of direct and inverse unreliable), WDE of long tubular bones of extremities (by 25.0 % of strong and average force of inverse reliable), cephalometric indicators (14.3 % of average force of inverse reliable and 28.6 % of average forces of inverse unreliability);

in women with a mild course of the disease - 44 correlations out of 59 possible (74.6 %), among which 1.7 % of the average strength of direct reliable, 3.4 % of strong inverse reliable, 33.9 % of the average strength of inverse reliable and 35.6 % of the average strength of inverse unreliable. The relative majority of correlations were established with total body sizes (33.3 % of the mean force of the inverse reliable and 66.7 % of the average force of the inverse unreliable), WDE of long tubular bones (75.0 % of the average force of the inverse reliable and 25.0 % of the average force of the inverse unreliable), sizes of the pelvis (by 25.0 % of reversible strong reliable and medium strength of unreliable and 50.0 % of average strength of inverse reliable), somatotype components (33.3 % of average strength of direct reliable and 66.7 % of average strength of inverse unreliable), indicators of component composition of body weight (25.0 % of average strength of inverse reliable and 75.0 % of the average force of the inverse unreliable), TSFF (by 44.4 % of the average force of the inverse reliable and unreliable), transverse torso dimensions (50.0 % of the average force of the inverse reliable and 25.0 % of the average force of the inverse unreliable), girth body sizes (by 33.3 % of the average force of the inverse reliable and unreliable and 6.7 % strong reverse reliable) and longitudinal body dimensions (60.0 % of the average force of the inverse unreliable);

in women with severe disease course - 23 correlations out of 59 possible (39.0 %), among which 1.7 % of the average strength of direct unreliable, 5.1 % of the average strength of reverse reliable and 32.2 % of the average strength of reverse unreliable. The relative majority of correlations are established with total body size (100 % of the mean force of inverse inaccuracies), indicators of the component composition of body weight (75.0 % of the average force of inverse unreliable), girth body sizes (46.7 % of the average force of the reverse unreliable) and longitudinal body sizes (20.0 % of the average force of the reverse reliable and unreliable).

The analysis of *OSIS* correlations with *anthropo-somatotypological* indicators of men and women with mild and severe seborrheic dermatitis revealed the following *multiple* reliable and moderate unreliable correlations:

in men with a mild course of the disease - moderate inverse (r = from -0.30 to -0.56), mostly unreliable, correlations with more than half of the cephalometric parameters, transverse torso size and TSFF, half of the WDE of the extremities and girth sizes and as a consequence with meso- and endomorphic component of somatotype and muscular components of body weight according to Matiegka and AIN;

in men with severe disease course - not found;

in women with a mild course of the disease - direct (r = from 0.32 to 0.77), mostly moderate, reliable and unreliable correlations with most cephalometric indicators, as well as inverse (r = from -0.31 to -0.62), mostly moderate, reliable and unreliable correlations with almost half of the girth size of the body, most of the transverse dimensions of the torso and a third of the indicators of TSFF;

in women with severe disease course - not found.

A *quantitative analysis of reliable and moderate unreliable correlations* in men and women with mild and severe seborrheic dermatitis between *OSIS* and *anthropo-somatotypological* indicators revealed the following distribution of correlations:

in men with a mild course of the disease - 26 correlations out of 58 possible (44.8 %), among which 1.7 % of the average strength of direct unreliable, 12.1 % of the average strength of reverse reliable and 31.0 % of the average strength of reverse unreliable. The relative majority of correlations were established with the components of the somatotype (33.3 % of the average force of the inverse reliable and 33.3 % of the average force of the direct and inverse unreliable), transverse torso sizes (25.0 % of the average force of the inverse reliable and 50.0 % of the average force of the inverse unreliable), cephalometric parameters (28.6 % of the average strength of the inverse reliable and unreliable), WDE of long tubular bones and indicators of the component composition of body weight (50.0 % of the average force of the inverse unreliable), girth body sizes (20.0 % of the average force of the inverse reliable and 26.7 % of the average force of the inverse unreliable) and TSFF (44.4 % of average force of return unreliable);

in men with severe disease course - 4 correlations out of 58 possible (6.9 %), among which 5.2 % of the average strength of direct unreliable and 1.7 % of the average strength of reverse unreliable. The relative majority of correlations are established with pelvic size (66.7 % of mean inverse unreliable strength);

in women with a mild course of the disease - 20 correlations out of 59 possible (33.9 %), including 1.7 % of

strong direct reliable, 1.7 % of the average strength of direct reliable, 10.2 % of the average strength of direct unreliable, 1.7 % of strong reverse reliable, 6.8 % of the average strength of the inverse reliable and 11.9 % of the average strength of the inverse unreliable. The relative majority of correlations were established with the transverse dimensions of the torso (25.0 % of the mean force of the inverse reliable and 50.0 % of the average force of the inverse inaccurate), cephalometric indicators (14.3 % of direct strong and medium strength of the reliable and 42.9 % of the direct force of the unreliable), somatotype components (by 33.3 % of the average force of direct and inverse unreliable) and girth body sizes (by 20.0 % of the average force of inverse reliable and unreliable and 6.7 % of strong inverse reliable);

in women with a severe course of the disease - 9 correlations out of 59 possible (15.3 %), among which 3.4 % of the average strength of direct unreliable, 1.7 % of the average strength of reverse reliable and 10.2 % of the average strength of reverse unreliable. The relative majority of correlations were established with TSFF (11.1 % of the average strength of the inverse reliable and 22.2 % of the average strength of the direct and inverse unreliable) and longitudinal body sizes (50.0 % of the average strength of the inverse unreliable).

Thus, founded correlations between men and women with seborrheic dermatitis, between OSSAS or OSIS and anthropo-somatotypological indicators, expands the current understanding of risk criteria and unfavorable prognosis of the disease.

Conclusion

1. When analyzing the correlations of OSSAS or OSIS with anthropo-somatotypological indicators of men and women with generalized fatty seborrheic dermatitis of mild and severe course, it was found that the predominant number of reliable or moderate unreliable (observed more often, except for OSSAS correlations with anthropo-somatopoietic dermatitis indicators in women with mild disease) correlations are reversible.

2. In the analysis of correlations of OSSAS or OSIS with anthropo-somatotypological indicators of men and women with seborrheic dermatitis of mild and severe course, it was found that regardless of sex, most reliable or moderately unreliable correlations are observed in mild disease.

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The introduction reflects the state of research and the relevance of the problem according to the world scientific literature (at least 15 references to English articles in international journals over the past 5 years). At the end of the entry, the purpose of the article is formulated (contains no more than 2-3 sentences, in which the problem or hypothesis is addressed, which is solved by the author).

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