treatment of patients with periodontitis combined with c dentition abnormalities and deformations. *Voennaya Meditsina*. 2013;1:103-107.
11. Rubnikovich S. P. Use of digital dynamic speckle anemometry for diagnosis of the surface blood flow in the mouth cavity tissue. *Stomatologicheskii Zhurnal*. 2007;3:26.
12. Rubnikovich S. P., Bazylev N. B., Fomin N. A. New possibilities of investigating blood flow in soft tissues of the mouth. *J. of Engineering Physics and Thermophysics*. 2008;81(3):533-543.
13. Rubnikovich S. P., Vladimirskaya R. E., Shved I. A. [et al.] Simulation of experimental periodontitis in animals. *Meditsinskii Zhurnal*. 2011;1:97-101.
14. Voichenko N. V. Comparison of magneto and magneto phototherapy in experimental arthritis. *Novosti Mediko-Biologicheskikh Nauk*. 2012;2:129-136.

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ANALGESIC ACTIVITY OF NEW DERIVATIVES OF QUINAZOLINONE-4

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АНАЛЬГЕЗИРУЮЩАЯ АКТИВНОСТЬ НОВЫХ ПРОИЗВОДНЫХ ХИНАЗОЛИНОНА-4

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In the of study was investigated the antinociceptive action of derivatives of quinazolinone-4 in 187 male and 196 female rats, including females rats in the different stages of the estrous cycle: diestrus ½ and proestrus /estrus in models of nociceptive responses induced by chemical stimuli (formalin test, «acetic cramps»), to assess the level of organization of the peripheral pain sensation. Substances (laboratory code numbers: PGFA – I, II, III, IV, V, VI, VII) at a dose of 2/10 of the molecular weight in mg/kg, reference drugs: metamizole sodium and lidocaine was administered once intraperitoneally 40 minutes before administration of chemical irritants. Control and males received respectively solubilizate Tween-80 and saline (0.4 ml intraperitoneally) under similar conditions. The 4-quinazolinone derivatives compounds I–IV, VI, VII were investigated as potential analgesics. Substance I–IV, VI, VII exhibited analgesic activity in male and female rats. Substances I, VI, VII have analgesic effects on female rats in phase of the estrous cycle diestrus ½; substance I–IV, VI – in the stage of proestrus/estrus. Among the investigated derivatives of quinazolinone-4 compound VI is a leader in analgesic activity.

Keywords: derivatives of quinazolinone-4, analgesic effect, formalin test, acetic cramps

Изучалось антиноцицептивное действие производных хиназолинон-4 у 187 самцов и 196 самок крыс, в том числе у самок в стадиях эстрального цикла: диэструс ½ и проэструс/эструс в формалиновом тесте, тесте «уксусные корчи». Вещества (лабораторные шифры: PGFA – I, II, III, IV, V, VI, VII) в дозе 2/10 от молекулярной массы в мг/кг, метамизол натрия и лидокаин вводили однократно внутрибрюшинно за 40 минут до введения альгогенов. Контрольные животные получали солюбилизат твина-80 и физиологический раствор. Производные хиназолинона-4 соединения I–IV, VI и VII оказались интересны в качестве потенциальных анальгетиков. Вещества I–IV, VI и VII проявляют обезболивающую активность у самцов и самок. Соединения I, VI и VII оказывают обезболивающее действие на самок крыс в фазе диэструс ½; вещества I–IV и VI – в стадии проэструс/эструс. Среди исследованных производных хиназолинона-4 соединение VI является лидером по анальгетической активности.

Ключевые слова: производные хиназолинона-4; обезболивающее действие, формалиновый тест, уксусные корчи

The creation of new, safe and highly effective drugs, including painkillers, is the actual problem of pharmacological and pharmaceutical science, the solution of which is possible result of synthesis and comprehensive studies of new biologically active compounds [5, 11, 12, 19]. Earlier, we in evaluation of the spectrum of pharmacological action of new derivatives of quinazolinone–4 we showed the antiparkinsonian activity, effect on blood clotting [6, 9, 10]. Given the differences in the activity of drugs based on gender, stages of the estrous cycle [1, 7, 8, 15, 18] the study was performed in male and female rats, including females in the different stages of the estrous cycle. The aim of this study was to investigate the antinociceptive action of derivatives of quinazolinone-4.

Material and Methods. The series of experiments were performed on white rats – males (187) and females (196) weighing 200-220g (6–12 per group) contained in standard vivarium conditions with natural light. At work with animals provided in full compliance with the international recommendations of the European Convention [2]. The analgesic activity of the compounds was determined in models of nociceptive responses induced by chemical stimulus (formalin test and «acetic cramps»), to assess the level of organization of the peripheral pain sensation [2].

Formalin test evaluates somatic pain caused with algogens. The test simulates the reactions, when developing operational skin incision. The first phase of the reaction develops immediately and characterized by the influence of the primary afferents pain, the second phase is delayed in time and is a pain caused by an inflammatory reaction. Hyperalgesia simulated subplantarian introduction 50 mkl of 2 % aqueous solution of formalin into the dorsum of the right hind paw. Record the number of pain reactions («flinches»: raising paw, licking, biting of the site of injection) after injection of formalin during the whole observation time, a differentiated acute (first 10 minutes) and inflammatory (from 10 to 60 minutes) phase of the nociceptive response. The analgesic activity of the compounds was evaluated in total, and also separately for phases I and II by reduction of the nociceptive response, reduced the number of pain reactions compared with the indices in the control animals, taken for 100 %.

Test «Acetic cramps» is an accepted model of visceral nociception and is aimed at studying the peripheral analgesic activity of new substances using the method of chemical stimulation of nociceptors of the peritoneum and evaluation of characteristic motor responses. «Cramps « as a response to pain response are specific behavioral responses resulting from the action of chemicals that irritate the serous membranes, manifested by contractions of abdominal muscles, alternating with their relaxation, stretching of the hind limbs, a deflection of the back, resembling the pain of peritonitis. The specific pain response induced by the intraperitoneal administration of acetic acid solution (1 % solution; 0.5 ml/100 g of body weight). Analgesic effect was evaluated by the decrease in the number of «cramps» in 15 minute observation period following the administration of acetic acid solution as a percentage data of the control group of animals, taken as 100 %.

Biologically active compounds (new derivatives of quinazolinone-4) – 7 substances synthesized in the Department of Organic Chemistry Pyatigorsk Medical and Pharmaceutical Institute [6, 9, 10]. Substances (laboratory code numbers: PGFA – I, II, III, IV, V, VI, VII) at a dose of 2/10 of the molecular weight in mg/kg (I – 47.6 mg/kg; II – 53.6 mg/kg; III – 53.6 mg/kg; IV – 53.6 mg/kg; V – 56.4 mg/kg; VI – 75.2 mg/kg; VII – 59.2 mg/kg), reference drugs at therapeutically effective doses: metamizole sodium – 55 mg/kg (Analgin solution for intravenous and intramuscular administration of 500 mg/ml 2 ml ampoule; «Moshimfarmpreparaty them. Semashko», Russia) and lidocaine – 1 mg/kg (ampoules 2 % 2 ml; «Dalkhimpharm», Russia) was administered once intraperitoneally 40 minutes before administration of chemical irritants. The dose of the studied compounds and drugs of comparison were selected based on the literature data and the method of titration of dose [3, 4]. Control females and males received respectively solubilizate Tween-80 and saline (0,4 ml intraperitoneally) under similar conditions. From female animals by vaginal strokes estimated stage of the estrous cycle: diestrus ½ and proestrus /estrus prior to testing [15]. Experiments were performed in the daytime. The results were statistically processed using computer software package «Excel» and «BIOSTAT» (S. A. Glantz, McGraw Hill, USA). Statistically significant differences were confirmed by Student's t-test, Kruskal-Wallis test, the U-Wilcoxon-Mann-Whitney test. Differences were considered statistically significant when $p<0.05$.

Results and Discussion. *The analgesic activity of derivatives of quinazolinone-4 in male rats.* When using the male test substances I-IV, VI, VII was a decrease in the number of pain reactions in General, throughout the period of testing with formalin, and in the first acute phase nociceptive response (Table 1). This reduction in the frequency «flinches» – uplifts paws, licking, biting the injection site – was significant when using solubilization substances I, III, IV, VI, VII, and also more pronounced compared to the effects of drugs comparison of metamizole sodium and lidocaine in the applied doses with the introduction of I, III, VI, VII substances. During the second inflammatory phase (the last 50 minutes of the test) the pain response to chemical stimulation of the observed decrease in the number of «flinches» was statistically significant for the compounds VI, VII and more distinct than with the use of metamizole sodium (Table 1).

Table 1

Effect of quinazolinone-4 derivatives on the parameters of the formalin test and «acetic cramps» in male rats (% of the control group data)

Substances	Formalin test			Acetic cramps
	All period	Phase 1 (10 minutes)	Phase 2 (50 minutes)	
I	56.6 *	47.0*	63.4	23.7**
II	71.96	66.31	75.98	28.2***+
III	47.0 **	21.2**	65.3	49.3**
IV	71.6*	51.2*	86.2	30.9***+
V	99.6	90.0	108.1	80.7
VI	36.3***	44.8*	30.2**	51.1*
VII	44.7***	42.8*	46.1*	25.0***
Metamizole sodium	61.1 **	78.9	48.5*	17.4***
Lidocaine	78.9	54.6	96.3	83.9

Reliably relative to the control group of male rats: * – $p<0.05$; ** – $p<0.01$; *** – $p < 0.001$; comparing males and females: + – $p<0.05$.

Derivatives of quinazolinone-4 have also limited the amount of «acetic cramp» in male rats. Shifts at the same time were statistically significant with the introduction of solutions of compounds I–IV, VI, VII, but less distinct than when administered metamizole sodium.

Thus, the compounds I–IV, VI, VII limited the number of pain responses in the formalin test and in the test «acetic writhing» in male rats, demonstrating analgesic activity.

The analgesic activity of derivatives of quinazolinone-4 in female rats. When using females of the studied compounds showed a statistically significant decrease in the number of pain responses was observed after the use of the substance VI as a whole, throughout all phases of testing with formalin, and also when using solubilisate substance III in the first acute phase nociceptive response (Table 2). The reduced rate of uplift paws, licking, biting the injection site on the background of compound VI were more pronounced in comparison with the effects of drugs comparison.

Table 2

Effect of quinazolinone-4 derivatives on the parameters of the formalin test and «acetic cramps» in female rats (% of the control group data)

Substances	Formalin test			Acetic cramps
	All period	Phase 1 (10 minutes)	Phase 2 (50 minutes)	
I	68.0	65.9	69.3	11.7***
II	71.3	64.5	75.2	45.6* +
III	111.0	42.9*	150.7	63.6
IV	96.7	71.9	111.1	75.6 +
V	96.2	71.0	110.8	82.0
VI	17.0**	29.1**	10.0*	19.5**
VII	43.5	49.2	40.2	32.0**
Metamizole sodium	28.4*	32.4*	26.0*	12.1***
Lidocaine	50.3	61.4	43.8	39.4*

Reliably relative to the control group of female rats: * – $p<0.05$; ** – $p<0.01$; *** – $p<0.001$; comparing males and females: + – $p<0.05$.

In the test «acetic cramps» 4-quinazolinone derivatives has limited the frequency of pain responses in female rats, statistically significant when using substances I, II, VI, VII. Thus the effect of substance I was more pronounced than when administered metamizole sodium and lidocaine, and compounds VI, VII more distinctly compared to the action of lidocaine. In intergroup comparisons, activity of the compounds studied in groups of males and females was found more pronounced analgesic effect of compounds II, IV in male animals.

Consequently, the compounds I, II, III, VI, VII reduced the frequency nocicarried out of the responses in the formalin test and in the test «acetic cramps» in female rats, exhibiting an analgesic action.

The analgesic activity of derivatives of quinazolinone-4 in female rats at different stages of the estrous cycle. When analyzing the analgesic activity of the studied substances in female animals, taking into account the phase of the estrous cycle in the stage of diestrus ½ revealed a decrease in the number of pain reactions in general and especially pronounced during the second inflammatory phase of formalin test using the substance VII (Table 3). However, during the second phase of the inflammatory response was observed nociceptive effect of substance IV when used in females in a state of physiological dormancy.

In the test «acetic cramps» derivatives of quinazolinone-4 limited the number of pain responses in female rats in a state of diestrus ½, statistically significant for the compounds I, VI, VII, but the effect of the substance was less pronounced than when administered the comparison drugs.

Thus, the compounds I, VI, VII exhibited analgesic activity in female rats at the stage of the estrous cycle diestrus ½ , limiting the number of pain reactions.

Table 3

Effect of quinazolinone-4 derivatives on the parameters of the formalin test and «acetic cramps» in female rats in stages diestrus ½ and proestrus/estrus (% of females according to the control groups in the respective stages of the estrous cycle)

Substances		Formalin test			Acetic cramps
		All period	Phase 1 (10 minutes)	Phase 2 (50 minutes)	
I	diestrus ½	152.3	108.3	205.0	22.4 *
	proestrus/estrus	51.6	52.8 *	50.9	3.8**
II	diestrus ½	128.4	85.4	180.0	60.1
	proestrus/estrus	57.4 *	55.6*	58.4	37.4*
III	diestrus ½	193.2	66.7	345.0	85.6
	proestrus/estrus	85.5	34.3**	111.0	44.1 *
IV	diestrus ½	285.5	140.0	460.0*	65.4
	proestrus/estrus	59.1	49.6	63.9	83.5
V	diestrus ½	273.6	116.7	462.0	79.6
	proestrus/estrus	61.6	58.5	63.2	91.1
VI	diestrus ½	33.6	41.7	24.0	16.8 *
	proestrus/estrus	14.9*	26.7**	9.0 *	23.7*
VII	diestrus ½	13.6 *	25.0	0 *	17.7*
	proestrus/estrus	57.97	65.43	54.21	49.4
Metamizole sodium	diestrus ½	72.7	60.0	88.0	9.1**
	proestrus/estrus	20.4*	23.7**	18.7 **	17.5*
Lidocaine	diestrus ½	153.4	137.5	172.5	9.25 *
	proestrus/estrus	31.5*	39*	28 **	46.8

Reliably relative to the control group of female rats: * – $p<0.05$; ** – $p<0.01$.

In female animals, who are in the stage of proestrus/estrus (a physiological stress phase), noted the decrease in the total number of pain reactions during the testing period with the introduction of the investigated compounds. The changes were statistically significant when using solutions of compounds II, VI. On the background of substance VI reducing the frequency of painful responses was clearer, than at introduction of preparations of comparison.

In the analysis of analgesic activity of the test substances in view of the test phases (inflammatory and acute), there was a significant limitation of the number of painful reactions in females in proestrus/estrus treated with solutions of the compounds I–III, IV (p=0,09), VI (Table 3). When using substance VI in the second inflammatory phase of formalin test was observed a significant reduction in the incidence of painful reactions are more pronounced in comparison with the action of metamizol sodium and lidocaine in female rats in a state of proestrus/estrus.

In the test «acetic cramps» derivatives of 4-quinazolinone limited number of «cramps» in female rats in proestrus/estrus, significantly when administered solutions of compounds I-III, VI. At the same substances the effects were more pronounced than when administered lidocaine, but inferior analgesic activity of Metamizole sodium.

Accordingly, the compounds I–IV, VI–VII show analgesic activity of female rats at the stage of the estrous cycle proestrus/estrus, reducing the amount of pain responses.

Thus, the study found executed in analgesic activity of novel quinazolinone-4 in the formalin test and in the test «acetic cramps» in male and female animals. This analgesic effect of substance VI was stable in males and females in both the used test methods, including females in the different phases of the estrous cycle, and is more pronounced than the activity of the compounds studied, and the comparison drugs metamizole sodium and lidocaine in males and females, and as females in state proestrus/estrus in the test with formalin. In the test, «acetic cramps» greatest analgesic effect observed upon administration of substance I in male and female animals, including in females in the phase of the estrous cycle proestrus/estrus, and this effect was more pronounced than the effects of metamizole sodium and lidocaine in General, females and females in the stage of proestrus/estrus.

One of the mechanisms of nocigenic action of formalin is the activation of TRPA1 channels (family of AC receptor potential channel) reacting normally to the cold, and stimulating the development of inflammation [16, 17]. On the other hand, as observed in the formalin test nonsteroidal antiinflammatory drugs inhibit only the second phase, and local anesthetics – only the first phase [2, 14]. As a result of the study compounds I–IV, VI, VII active during the first phase of the formalin test, so it can be assumed that the substance exhibit antinociceptive action, exerting local anesthetic effect. Compound VI is blocked and the second phase of the test in male and female rats and substance VII suppressed the second test phase in males and in females in a state of diestrus ½, suggesting that the mechanism of the analgesic action of substances VI–VII possible combination of local anesthetic and anti-inflammatory activity. Furthermore, it can be assumed implementation analgesic activity of the test substances when exposed to the C-polymodal nociceptors are sensitive to chemical stimuli, particularly to formalin and sensitizing with inflammation and tissue injury [20].

Installed sex differences in antinociceptive activity of the compounds II, IV (most pronounced analgesic effect in males compared with females), explains the possibility of the influence of sex hormones [1, 7, 8, 18], consistent with observations of a more powerful and efficient action of butorphanol in males than in females rodents and primates [13], which was interpreted as genetic differences in the formation of sex chromosomes [18]. Award-most manifestation of the analgesic action of the compounds in the female rats in the stage of the estrous cycle proestrus/estrus than in diestrus ½, can probably be explained by the greater sensitivity of the female body in a physiological stress period [15].

Conclusions. The 4-quinazolinone derivatives compounds I–IV, VI, VII were interesting as potential analgesics. Substance I–IV, VI, VII in a dose of 2/10 of the molecular weight in mg/kg exhibit analgesic activity in male and female rats in test models of visceral inflammatory pain (formalin test, «acetic cramps»). Substances I, VI, VII have analgesic effects on female rats in phase of the estrous cycle diestrus ½; substance I–IV, VI – in the stage of proestrus/estrus. Among the investigated derivatives of quinazolinone-4 compound VI is a leader in analgesic activity.

References

1. Baturin V. A., Manvelyan E. A., Bulgakova M. D. Zavisimost ot pola i vremeni sutok intensivnosti galoperidolovoy katalepsii u krys. *Biomeditsina. – Biomedicine.* 2006;1(4):78-79.
2. Voronina T. A., Guzevatykh L. S. Metodicheskiye rekomendatsii po izucheniyu analgeticheskoy aktivnosti lekarstvennykh sredstv. Rukovodstvo po provedeniyu doklinicheskikh issledovany lekarstvennykh sredstv. Pod obsh. red. A.N. Mironova. M.: «Grif i K»; 2012.
3. Galenko-Yaroshevsky A. P., Anisimova V. A., Minkin V. I., Tolpygin I. Ye., Varlashkina I. A. [et al.] Sredstvo, obladayushcheye mestnoanesteziruyushchim deystviyem. Patent na izobreteniye. RUS 2006140600/15 16.11.2006.
4. Dubrovin A. N., Mikhalev A. I., Ukhov S. V., Konshina T. M., Vakhrina N. I. [et al.] Sintez i svoystva 2-zameshchennykh amidov tsinkhoninovoy kisloty. *Sovremennye problemy nauki i obrazovaniya. – Modern problems of science and education*. 2012;4. Available at: https://science-education.ru/ru/article/view?id=6630
5. Emelyanova T. G., Guzevatykh L. S., Chulichkov A. L., Guzevatykh A. P., Voronina T.A. Protivovospalitelnaya i analgeticheskaya aktivnosti dipeptida Tyr-Pro i ego analogov. *Akademichesky zhurnal Zapadnoy Sibiri. – Academic Journal of Western Siberia.* 2014;10(4):88-89.
6. Manvelyan M. M., Prizova Ye.Yu., Semenova I. A. [et al.] Vliyaniye proizvodnykh khinazolinona-4 na svertyvayushchuyu sposobnost krovi. *Farmatsiya i farmakologiya. – Pharmacy and Pharmacology*. 2015;3(S):70-71.
7. Manvelyan E. A., Sysa V. Yu., Kodonidi I. P., Oganesyan E. T., Bandura A. F., Sochnev V. S. Influence of o-benzoilaminobenzoic acid amides, derivative precursors of quinazolinone-4, on the behavior of male rats in the elevated plus maze. *Medical News of North Caucasus.* 2014;9(4):378-379. doi: 10.14300/mnnc.2014.09035
8. Manvelyan E. A., Anisimova N. A. Tsirkadiannye razlichiya effektivnosti diazepama u stressirovannykh samok i samtsov krys. *Nauka. Innovatsii. Tekhnologii. – The science. Innovation. Technologies*. 2011;3:46-52.
9. Manvelyan E. A., Manvelyan M. M. Poisk veshchestv s protivoparkinsonicheskim deystviyem v ryadu novykh sintezirovannykh proizvodnykh khinazolinona-4. *Eksperimentalnaya i klinicheskaya farmakologiya. – Experimental and Clinical Pharmacology*. 2015;78(S):42.
10. Ovakimyan A. G., Bicherov A. A., Kodonidi I. P. [et al.]. Prognoz, sintez i izucheniye dofaminergicheskoy aktivnosti gidroksi- i metoksifenilnykh proizvodnykh 4-(3)khinazolinona. *Sovremennye problemy nauki i obrazovaniya. – Modern problems of science and education*. 2015;2(2):511. Available at: http://www.science-education.ru/ru/article/view?id=23168.
11. Alexander S. P. H, Davenport A. P., Kelly E., Marrion N., Peters J. [et al.] CGTP Collaborators. The Concise Guide to PHARMACOLOGY 2015/16: G Protein-Coupled Receptors. *British Journal of Pharmacology.* 2015;172:5744-5869. doi: 10.1111/bph.13348
12. Al-Hasani R., Bruchas M. R. Molecular Mechanisms of Opioid Receptor-Dependent Signaling and Behavior. *Anesthesiology.* 2011;115:1363-1381.
13. Guzman D. S., Drazenovich T. L., KuKanich B., Olsen G. H. Evaluation of thermal antinociceptive effects and pharmacokinetics after intramuscular administration of butorphanol tartrate to American kestrels (Falco sparverius). *American journal of veterinary research.* 2014;75(1):11-18.
14. Hunskaar S., Hole K. The formalin test in mice: dissociation between inflammatory and noninflammatory pain. *Pain.* 1987;30(1):103-114.
15. Manvelyan E. A., Baturin V. A. Dependence of intensity haloperidol' s catalepsy from time of day and stage of an estrus cycle on rat's. 2-nd Russian – Chinese International scientific conference on pharmacology. Fundamental pharmacology and pharmacy – clinical practice, September 2006; Perm: Perm State Pharmaceutical Academy; 2006. 113.
16. McNamara C. R., Mandel-Brehm J., Bautista D. M., [et al.] TRPA1 mediates formalin-induced pain. *Proc. Nat. Acad. Sci. USA.* 2007;104(33):13525-13530.
17. Nilius B., Owsianik G., Voets T., Peters J. A. Transient receptor potential cation channels in disease. *Physiol. Rev.* 2007;87(1):165-217.

18. Russell S. E., Rachlin A. B., Smith K. L., Muschamp J. Sex Differences in Sensitivity to the Depressive-like Effects of the Kappa Opioid Receptor Agonist U-50488 in Rats. *Biological psychiatry.* 2013:1-10.
19. Simonson B., Morani A. S., Ewald A. W. M., Walker L., Kumar N. [et al.] Pharmacology and anti-addiction effects of the novel κ opioid receptor agonist Mesyl Sal B, a potent and long-acting analogue of salvinorin A. *British Journal of Pharmacology.* 2015;172:515-531.
20. Smith E. S., Lewin G. R. Nociceptors: a phylogenetic view. *J. Comp. Physiol. A. Neuroethol. Sens. Neural. Behav. Physiol.* 2009;195(12):1089-1106.

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CORRECTION OF INITIAL CEREBRAL DISORDERS IN ARTERIAL HYPERTENSION

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КОРРЕКЦИЯ НАЧАЛЬНЫХ ЦЕРЕБРАЛЬНЫХ НАРУШЕНИЙ ПРИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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A comprehensive examination of 114 patients with stage I and II hypertension was carried out. The aim of the study was to develop a modern, pathogenetically substantiated, comprehensive non-medicamentous method of curative correction of early cerebral manifestations of hypertension. The main correction of the initial manifestations of hypertension was a special technique of curative gymnastics and respiratory gymnastics with elements of group psychotherapy. Group 1 (n=80) – patients who received complex non-drug treatment; Group 2 (n=34) – patients who received drug-induced antihypertensive therapy on the basis of monotherapy or low-dose combination therapy. Patients of the 1 st group reported a significant (p<0.01) improvement after the end of treatment. Intergroup differences obtained before and after treatment, in patients of the 1 st and 2 nd groups it had a significant (p<0.01) nature. The study of cerebral hemodynamics significantly (p<0.01) indicated an increase in the majority of patients of the 1st group of blood flow along the vertebral arteries, the posterior cerebral arteries. In the state of vasomotor reactivity and autoregulation of cerebral blood flow, there was significant (p<0.01) positive dynamics only in patients of the 1st group. Thus, the analysis of the results of our algorithm for treating patients with initial manifestations of hypertension, conducted with the use of non-drug methods, demonstrates the validity of the proposed pathogenetic approach to ongoing therapy.

Keywords: arterial hypertension, therapy, combined therapy, nonmedical methods

Было проведено комплексное обследование 114 пациентов с АГ I и II стадии. Цель исследования – разработать современный патогенетически обоснованный комплексный немедикаментозный метод лечебной коррекции ранних церебральных проявлений артериальной гипертензии (АГ). Основой коррекции начальных проявлений АГ являлась специальная методика лечебной гимнастики и дыхательной гимнастики с элементами групповой психотерапии. 1-я группа (n=80) – пациенты, получавшие комплексное немедикаментозное лечение; 2-я группа (n=34) – пациенты, получавшие медикаментозную гипотензивную терапию на основе монотерапии или низкодозированной комбинированной терапии. Пациенты 1-й группы отмечали достоверное (p<0,01) улучшение после окончания лечения. Исследование церебральной гемодинамики достоверно (p<0,01) свидетельствовало об улучшении мозгового кровотока. В состоянии вазомоторной реактивности и ауторегуляции мозгового кровотока также отмечалась достоверная (p<0,01) положительная динамика только