DOI 10.26724/2079-8334-2023-2-84-203-208
UDC 616.831-007.17:616-036.838:616.89-008.454]-092+557.146.1

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MEXIDOL AND VORTIOXETINE ADMINISTRATION ENCOURAGING RESULTS IN EXPERIMENTAL POST-STROKE DEPRESSION COMPLEX TREATMENT

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The purpose of the study was to investigate the efficacy of combined mexidol and vortioxetine administration in conditions of experimental chronic brain ischemia. 65 rats were randomized into 5 groups, respectively, due to induced chronic brain ischemia and its correction using mexidol and vortioxetine separate and combined administration. The neurological deficits expression, the ability to form the conditioned reflexes of active avoidance, short-term and long-term memory keeping as well as the aggressive-defensive behaviour were studied in rats throughout the post-ischemic period. 1 day of the trial revealed immobility and neurological deficit in rats accompanied by cognitive disorders and the emotional behaviour disturbance. An expressed anti-ischemic effect in the case of simultaneous mexidol endonasal administration and vortioxetine systemic was shown. Both mexidol and vortioxetine combined administration was proved to make a significant contribution to neurological deficits recovery, the memory disorders elimination and the aggressive-protective behaviour normalization in animals during the post-ischemic state. The authors considered that the positive results of the effective use of mexidol and the multimodal antidepressant vortioxetine which are manifested by neurological deficits and mnestic functions restoration together with the emotional sphere normalization in ischemic conditions allow to recommend these compounds use in functional disorders complex correction in patients with ischemic strokes at the rehabilitation stage.

Key words: stroke, post-stroke depression, motor deficit, cognitive impairment, mexidol, vortioxetine, pathophysiological mechanisms, rehabilitation

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ОБНАДІЙЛИВІ РЕЗУЛЬТАТИ КОМПЛЕКСНОГО ЛІКУВАННЯ ЕКСПЕРИМЕНТАЛЬНОЇ ПОСТІНСУЛЬТНОЇ ДЕПРЕСІЇ ВВЕДЕННЯМ МЕКСИДОЛУ ТА ВОРТІОКСЕТИНУ

Метою дослідження було вивчення ефективності сумісного введення мексидолу та вортіоксетину в умовах експериментальної хронічної ішемії головного мозку. 65 щурів були розділені на 5 групи відповідно відтвореної хронічної ішемії мозку та її корекції шляхом роздільного та сумісного введення мексидолу та вортіоксетину. В постішемічному періоду у щурів досліджували вираженість неврологічного дефіциту, здатність до утворення умовних рефлексів активного уникнення, зберігання коротко- та довгочасної пам'яті, а також вираженість агресивно-захисної поведінки. На 1 добі досліду в щурів реєструється знерухомленість та неврологічний дефіцит, що супроводжується мне стичними розладами та порушенням емоційної сфери. Висвітлено виражений протиішемічний ефект в разі сумісного ендоназального введення мексидолу та системного введення вортіоксетину. Доведено, що сумісне введення мексидолу та вортіоксетину сприяло відновленню неврологічного дефіциту, усуненню мнестичних розладів та нормалізації агресивно-захисної поведінки тварин в постішемічному стані. Автори вважають, що позитивні результати ефективного застосування мексидолу та мультимодального антидепресанту вортіоксетину, які проявляються відновленням неврологічного дефіциту та мнестичних функцій, нормалізацією емоційної сфери за умов ішемізації дозволяють рекомендувати застосувати ці сполуки при комплексній корекції функціональних розладів у хворих з ішемічними інсультами на реабілітаційному етапі.

Ключові слова: інсульт, постінсультна депресія, моторний дефіцит, когнітивні порушення, мексидол, вортіоксетин, патофізіологічні механізми, реабілітація

The study is a fragment of the research project "To investigate the chronic convulsive syndrome pathogenetic mechanisms on the model of pharmacological kindling and to study the efficacy of its complex pathogenetical correction by anticonvulsant mechanisms activation", state registration No. 0122U000081.

The incidence of cardiovascular pathology has already acquired catastrophic indicators with ever-increasing varieties and complications [6]. Experts are worrying about the increasing number of comorbid pathology episodes against the background of manifesting chronic brain ischemia (CBI) [9, 14]. Chronic brain ischemia remains one of the most common cerebrovascular diseases, and its progression becomes a hard medical trouble associated with the efforts of early diagnosis, adequate complex pathogenetically oriented treatment and effective rehabilitation since this disease causes social maladjustment of a significant contingent of patients [12].

Complex and diverse CBI etiological factors including myocardial disease, atherosclerotic lesions of the vascular wall, endocrinopathies, neural disorders, uncontrolled arterial hypertension, etc. together with complex prolonged chains of CBI pathophysiological mechanisms with vital organs and systems involvement into the mediation of pathological process put forward multifarious requirements regarding these patients rehabilitation process [5, 10, 12]. We considered reasonable to take into account the cerebral blood circulation

acute and chronic microcirculatory disorders, main vessels tortuosity, heart failure, coagulopathy, hereditary factors and degenerative diseases, etc. presence in the CBI pathogenesis and clinical picture that increase the degree of neurons damage in ischemic disorders and form general postischemic depressive manifestations [10].

It is clear that all mentioned above is taken into account when treatment complex schemes performing and therefore should be reflected in the prolonged rehabilitative process for the sanogenetic mechanisms efficient activation. We made attempts to develop a personalized scheme of the certain contingent of patients with CBI rehabilitation with accompanying neurological and cognitive disorders, which also form the basis of post-ischemic depression, but we finally decided firstly to provide the experimental studies which results we will take as the basis for subsequent clinical trials and rehabilitation measures.

The purpose of the study was to investigate the efficacy of combined mexidol and vortioxetine administration in conditions of experimental chronic brain ischemia treatment.

Materials and methods. Experimental studies were performed on 65 white matured male Wistar rats. The animals were kept in standard vivarium conditions. Experimental animals keeping and manipulation was done in accordance with the "General Ethical Principles of Animal Experiments" adopted by the Fifth National Congress on Bioethics (Kyiv, 2013) and was guided by the recommendations of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1985) and guidelines of the State Pharmacological Center of the Ministry of Health of Ukraine on "Preclinical studies of drugs" (2001) as well as rules of humane treatment of experimental animals and conditions approved by the Committee on Bioethics of Odesa National Medical University (Prot. N17-C from 12.10.2021).

Chronic brain ischemia was reproduced by skin dissection, carotid arteries bilateral selection ligation [5]. 5 groups of animals were randomized: 1 group - control (intact rats with only skin dissection, n=9). Group 2 – trial (rats with carotid arteries ligation and CBI reproduction, n=15). Group 3 – rats with CBI with mexidol (MD, "Stada Artsnaimittel AG", Germany; 5.0 %, intranasally, 10 μl, n=15) administered. Vortioxetine (VX; "Lundbeck", Denmark; 5.0 mg/kg, subcutaneously, n=15) was administered to rats of the 4th group with CBI. Rats of the 5th group (n=11) with CBI were simultaneously injected with MP and BRT.

Rats were observed for 7 days after the carotid arteries ligation. Neurological status of rats with CBI during this time was assessed by evaluating the expression of neurological deficits according to the scale for motor changes estimation [8].

Mnestic functions in rats with CBI were tested by conditioned active avoidance reactions (CAAR) forming in them in a rectangular chamber (50x15 cm) with metal walls 40 cm high and a metal floor connected to a source of electric current. The chamber was divided into 2 equal parts (25x15 cm each) by a wall with a door that could be lowered manually. 20 W lamps were installed in each compartment. Turning on the light was used as a conditioned signal (CS). An electric current with strength of 0.5–0.8 mA, which was fed through the metal floor, served as the unconditional signal (US) [7]. The learning keeping in memory was checked after 24 hrs (short-term memory) and after 7 days (long-term memory) in a similar way by presenting firstly the CS followed by the US [7].

The emotional-aggressive behaviour expression was evaluated according to a generally accepted 5-point scale which takes into account the nature of the behavioural response of animals to an attempt to take the researcher's hand [13].

The data obtained were statistically analyzed with the help of parametric ANOVA test followed by Newman-Keulls test and the non-parametric Krushkal-Wallis test. The minimal statistical probability was determined at $p<0.05$.

Results of the study and their discussion. Motor activity of rats with CBI was characterized by hypodynamia which was identical in case of vertical and horizontal motor activity studying. Rats with CMI demonstrated constant left- and right-side rotations with an average frequency of 5 to 7 per minute. We found the maximal number of rotations on the 3rd day of the trial – 5.8±0.7, the number of rotations during the entire observation period did not change significantly (Table 1).

While examining the neurological deficit expression, none of the control rats showed lethargy, slowness and weakness of movements, "manege movements", limbs paresis and paralysis. 1 day after the CBI reproduction 14 rats out of 15 showed lethargy and slowness of movements, all rats showed weakness of movements, 9 rats showed "manage movements" which was significantly extra compared with the corresponding indexes in the control group ($P<0.01$). Motor deficits in the form of paresis and/or paralysis were also present in a greater number of rats ($P<0.01$). Similar results without dynamics were registered during the entire observation period. We did not register any changes in the studied indexes in CBI rats on the 1st day of the trial after separate and combined MD and VX administration.

Table 1

The influence effect of mexidol (MD) and vortioxetine (VX) separate and combined administration on the neurological deficit expression (%) in rats with chronic brain ischemia (CBI)

Groups of animals	Lethargy and slowness of movement	Weakness of movements	"Manege" movements	Paresis of 1-4 limbs	Paralysis of 1-4 limbs
Day 1					
Control, n=9	0	0	0	0	0
CBI, n=15	93**	100**	60**	87**	20**
CBI +MD, n=15	93**	100**	60**	87**	13**
CBI +VX, n=15	93**	100**	60**	87**	20**
CBI + MD+ VX, n=11	82**	82**	64**	82**	9**
Day 3					
Control, n=9	0	0	0	0	0
CBI, n=12	75**	100**	67**	75**	75**
CBI +MD, n=13	62*	77**	62**	62**	23#
CBI +VX, n=12	75**	83**	58*	58*	50*
CBI + MD+ VX, n=10	40* # @@@	40* # @ @@	20 # @@@	20 ## @@@	10 ##@@
Day 5					
Control, n=9	0	0	0	0	0
CBI, n=11	73**	73**	64**	55**	36**
CBI +MD, n=12	17##	17##	25##	0##	0##
CBI +VX, n=11	45*	55**	27*	36*	18*
CBI + MD+ VX, n=10	20 ##@@	20 ##@@	10 ## @@@	0 ##@@	
Day 7					
Control, n=9	0	14	0	0	0
CBI, n=10	60**	60**	50**	30**	30**
CBI +MD, n=12	8##	8##	8#	0#	0#
CBI +VX, n=11	27* #	45**	27 ##	0#	0#
CBI + MD+ VX, n=10	0 ##@@	0 ##@@	0 ##@@	0 ##	0 ##

Notes are the same in Tables 1 and 2: the decrease in the number of rats in the groups occurred due to their death; * – $P<0.05$ and ** – $P<0.01$ – statistical differences of the investigated parameters compared with the same in the control group (ANOVA + Newmann Keuls criteria); # – $P<0.05$ and ## – $P<0.01$ – statistical differences of the investigated parameters compared with the same in rats with CBI without the pharmacological correction (ANOVA + Newmann Keuls criteria); @ – $P<0.05$ – statistical differences of the investigated parameters compared with the same in CBI rats with MD administration (Kruscall-Wallis criterion); @@ – $P<0.05$ – statistical differences of the investigated parameters compared with the same in CBI rats with VX administration (Kruscall-Wallis criterion).

On the 3rd day of the trial the most pronounced effect of the evaluated neurological disorders normalization was achieved in CBI rats with combined MD and VX administered. Thus, lethargy and slowness of movements were registered only in 4 rats out of 10 which was significantly different from such index in CBI rats without treatment, as well as from similar indexes in CBI rats which were separately administered MD and VX (in all cases $P<0.05$). The rests indexes were also significantly different from the same data in rats of these groups. The striking effect of treatment complex with MD and VX was observed until the end of the trials.

On the 5th day of the trial positive effects in the form of all neurological disorders normalization in rats with CMI were obtained in rats with intranasal MD administration (in all cases $P<0.01$). This effect was also recorded till the 7th day of the trial. The studied criteria of neurological deficit normalization in CBI rats with VZ administration was achieved later, on the 7th day of the trial (in all cases $P<0.05$).

While studying the mnestic functions it was established that CBI rats required 33.4±3.4 CS and US combinations necessary for the CAAR occurrence which exceeded the corresponding control index ($P<0.05$, Table 2). The number of CS and US combinations required for the CAAR occurrence 1 day after the conditioned reflex development in rats in the conditions of the experiment was 11.2±1.1, and after 7 days – 5.4±0.6 which was 1.6 times and 2 times higher pertaining the same indexes in control group ($P<0.05$).

In case of MD and VX combined administration a significant decrease in the number of CS and US combinations necessary for the CAAR formation was registered on the 3rd day of the trial and continued until its end ($P<0.05$). The statistical probability of MD and VX combined administration efficacy comparing with the same indexes in case of their separate injection was reached on the 5th day of the trial and lasted until the end of the experiment ($P<0.05$).

Table 2

The influence effect of mexidol (MD) and vortioxetine (VX) separate and combined administration on the learning process expression, short-term and long-term memory in rats with chronic brain ischemia (CBI)

Groups of animals	The number of combinations of conditioned and unconditioned stimuli necessary for the conditioned reflex of active avoidance formation		
	Learning	Short-term memory	Long- term memory
Day 1			
Control, n=9	23.9±2.5	6.8±0.9	2.7±0.4
CBI, n=15	33.4±3.4*	11.2±1.1*	5.4±0.6**
CBI +MD, n=15	30.6±3.1*	10.4±1.1*	4.4±0.5*
CBI +VX, n=15	32.7±3.2*	11.5±1.2*	5.1±0.5*
CBI + MD+ VX, n=11	27.8±2.8	9.6±0.9	4.1±0.5
Day 3			
Control, n=9	23.9±2.5	6.8±0.9	2.7±0.4
CBI, n=12	39.1±3.8*	17.2±1.8**	8.1±0.8**
CBI +MD, n=13	26.3±2.7#	11.7±1.2*	7.1±0.7*
CBI +VX, n=12	30.6±3.1*	13.4±1.2*	6.4±0.5*
CBI + MD+ VX, n=10	25.7±2.4#	8.7±0.8#@	4.1±0.5@@@
Day 5			
Control, n=9	23.9±2.5	6.8±0.9	2.7±0.4
CBI, n=11	36.4±3.5*	15.3±1.6**	7.6±0.8**
CBI +MD, n=12	25.6±2.6#	8.4±0.9#	5.3±0.5*
CBI +VX, n=11	31.4±2.9*	12.7±1.1*	6.4±0.5*
CBI + MD+ VX, n=10	24.3±2.4#@@	7.6±0.7##@@	3.7±0.4@@@
Day 7			
Control, n=9	23.9±2.5	6.8±0.9	2.7±0.4
CBI, n=10	32.9±3.3*	13.1±1.5*	7.1±078**
CBI +MD, n=12	26.1±2.7	7.6±0.8#	5.6±0.5*
CBI +VX, n=11	28.8±2.9	10.3±1.2	6.7±0.6*
CBI + MD+ VX, n=10	23.7±2.3#@@	7.2±0.7#@@	3.2±0.3##@@@

A similar dynamic of the short-term memory expression was observed in case of MD and XT combined administration, however, it should be noted that in these model conditions the long-term memory recovery was recorded only on the 7th day of the trial. When the researcher's hand approached the intact rats, the animals avoided it, tried to bite and vocalized intensively. The average index of aggressive-defensive behaviour during the whole period of the study equaled 4 points (Fig. 1). During the entire period of the trial the CBI rats were in a depressed state and practically did not respond to the presence of the researcher's hand, the expression of their aggressive-protective behaviour was significantly less comparing with the same control index (P<0.01).

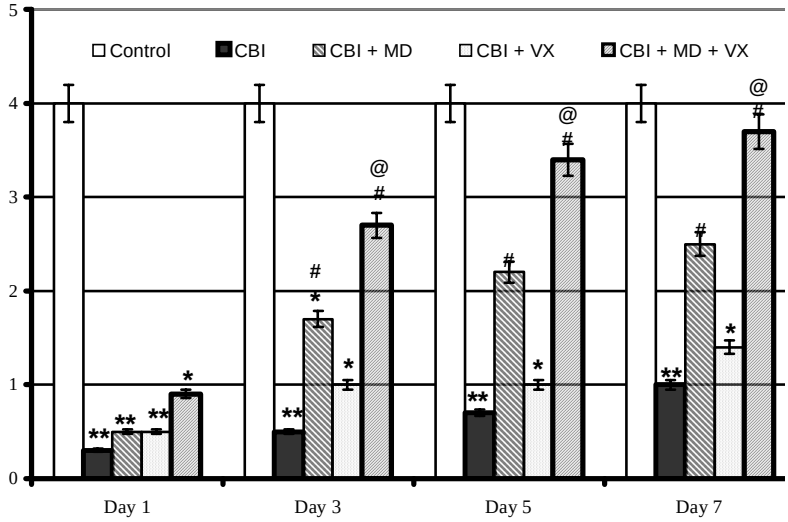

Fig. 1. The influence effect of mexidol (MD) and vortioxetine (VX) separate and combined administration on the emotional-aggressive behaviour expression in rats with chronic brain ischemia (CBI); * – P<0.05 and ** – P<0.01 – statistical differences of the investigated parameters compared with the same in the control group (ANOVA + Newmann Keuls criteria); # – P<0.05 – statistical differences of the investigated parameters compared with the same in rats with CBI without the pharmacological correction (ANOVA + Newmann Keuls criteria); @ – P<0.05 – statistical differences of the investigated parameters compared with the same in CBI rats with MD/VX administration (Kruscall-Wallis criterion).

Being injected separately MD reduced the severity of aggressive-defensive behaviour in CBI rats on the 3rd day of the trial (P<0.05) but this index remained to be lower than the same in the control group (P<0.05). On the 5th and 7th days the average expression of aggressive-defensive behaviour in CBI rats after MD administration was comparable to analogous control data.

Vortioxetine did not affect the studied index during the entire period of the trial, however, the significant differences in aggressive-defensive behaviour expression were achieved in conditions of MD

and VX combined administration – such behaviour index exceeded the same in CBI rats with the applied drugs separate administration ($P<0.05$).

Thus, the data obtained indicate a marked anti-ischemic effect achieved in experimental conditions in case of MD and VX combined administration. A preliminary conclusion about the applied complex efficacy is possible since MD and VX combined administration contributed to neurological deficits recovery, the elimination of memory disorders and the aggressive-protective behaviour normalization in CBI animals throughout the post-ischemic period.

We consider the obtained range of data interesting and important from the following points. Firstly, we believe to be fundamentally important to achieve a pronounced anti-ischemic effect in the case of MD endonasal administration. At the same time, we emphasize that MD was chosen taking into account its neuroprotective and antistress profile of properties [2, 15]. The pharmacon endonasal route of administration is known and promising, in our opinion, taking into account its higher rate of delivery directly to the brain which is extremely important in brain ischemia [2]. We are sure that any pharmacological drug penetration into the CNS efficacy in case of intranasal administration is significantly higher pertaining its systemic route of injection, and in this case, a particular compound avoids the possibility of blood-brain barrier passage which is encouraging from a pharmacokinetic point of view and promising from the point of view of the desired compound with neuroprotective properties higher intracerebral concentration faster obtaining to achieve the desired effect throughout the postischemic state.

Secondly, VX we choose as post-ischemic state treatment complex component due to a number of reasons, one of which is the observed both depressive behavioural and functional disorders formation during the post-ischemic period which significantly worsens its clinical manifestation and complicates the comorbid picture of post-ischemic depression [11]. The obtained effect of CBI animals memory functions improvement as a result of the comprehensive treatment confirms the validity of our assumption and the correctness of the selected composition of the pharmacological treatment which we consider justified from a pathophysiological point of view. Analyzing the obtained data concerning the learning normalization, as well as the short- and long-term memory restoration in CBI rats in conditions of multimodal antidepressant VX additional use, which, along its antidepressive, has also the anxiolytic and procognitive effects, a reduction in obsessiveness and compulsivity, as well as suicidality [11], we consider to be pathogenetically justified its use in the case of postischemic depression formation.

Thirdly, the perspective rehabilitative actions for patients with CBI should take into account the entire spectrum of clinical disorders, they should be personalized and adequately affects the established links of pathogenesis. Neurological deficits and mnestic dysfunctions restoration, the emotional sphere normalization in conditions of ischemia is a difficult task for the entire period of treatment and rehabilitation recovery. We consider it interesting from a scientific point of view and promising from a clinical point of view, to check the possibility of combined use of VX systemic administration and MD endonasal route of administration, as a certain efficacy of their combined administration has already been experimentally proven [1]. We supposed it's difficult to assess the contribution of each of these two drugs into a positive effect achievement but we note that from a clinical point of view the most important are the MD antioxidant, membrane-protective and neuroprotective effects, as well as the VX interaction with five subtypes of serotonin receptors – 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_3 та 5-HT_7, the first of which – 5-HT_{1A} – mediates the pathogenetic mechanisms of depression [11].

Therefore, the identical positive results of VX effective use in depressive disorders in epilepsy complex treatment [4] and MD endonasal administration successful use in CBI [3] allow us to recommend confidently these two compounds clinical use in case of functional disorders complex correction in patients with ischemic strokes at the rehabilitation stage.

Conclusions

1. The pronounced experimental anti-ischemic effect in case of combined MD endonasal administration and VX systemic administration is shown.

2. The combined MD and VX administration contributed to neurological deficits recovery, the memory disorders elimination and the aggressive-protective behaviour normalization in animals throughout the post-ischemic state which generally abolished the post-stroke depression manifestations.

3. The positive results of the effective use of MD with antioxidant, membrane-protective and neuroprotective action and the multimodal antidepressant VX with anxiolytic and procognitive effects

which are manifested by neurological deficits and mnestic functions restoration together with the emotional sphere normalization in ischemic conditions allow to recommend these compounds use in functional disorders complex correction in patients with ischemic strokes at the rehabilitation stage.

Prospects for further research include a further investigation of the experimental peculiarities of the of post-ischemic disorders correction rehabilitative scheme with the aim of neuroprotective scheme clinical efficacy evaluation in patients throughput the period of rehabilitative treatment.

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Стаття надійшла 19.04.2022 р.