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ANALYSIS OF THE NEUROLOGIC DEFICIT UNDER THE TRAUMATIC BRAIN INJURY AND METHODS OF ITS CORRECTION

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Abstract

Objective of the research. Provide the analysis of the neurologic deficit in dynamics under the experimental traumatic brain injury and methods of its correction by Carbacetam. **Materials and the methods of research**. The research was held by means of the white outbred male rats, aged six months, weighing 180-220 g, which were kept on a standard diet with free access to food and water in vivarium conditions. The modulation of the traumatic brain injury was based on the method of V.M. Eslki and S.V. Ziablitsev (2005), where the TBI was caused due to gravity load on animals' fixed heads. The process was held in compliance with the Helsinki Declaration adopted by the General Assembly of the World Medical Association, the general rules and principles of the European Convention for the Protection of Vertebrate Animals. The rats of experimental group 1 and 2 were analyzed based on the impact of Carbacetam and Actovegine onto TBI provided in recommended therapeutic dozes, i.e. intraperitoneally at a dose of 5 mg and 16 mg per kilogram of animal accordingly during 7 days. The comparison group consisted of the rats that were treated by the same manipulations as the above-mentioned experimental groups; however, 1 ml of saline was administered intraperitoneally instead of the experimental medicines. The following indicators were analyzed in 24 h, three days and a week based on 100 score scale: level of

consciousness; status of reflex area, including the width and the reaction of pupils to light, corneal reflex, hearing, muscle tone of the body and the reaction to light and pain; breath; movements and some behavioral reactions. **Outcomes and conclusions**. The data received pointed to moderate but feasible recovery of the neurological symptoms of rats under Carbatsetam in three days and a week of treatment in the reflex area, behavior and consciousness. Actovegine had significantly greater effect against the action of Carbatsetam in the motoric area. This can be used in the development of guidelines for the treatment and rehabilitation of the patients suffering TBI, depending on the scope of the major neurological disorders.

Keywords: Neurologic Deficit, Traumatic Brain Injury, Carbacetam.

Introduction. The degree of disability and quality of life, social adaptation of patients with traumatic brain injury (TBI) is determined by the severity of neurological disorders and psychological status [5, 7]. In some cases, the post-traumatic encephalopathy develops as a result of TBI. The severity of it does not always depend on the severity of a previous head injury – concussion may even lead to the development of atrophic processes, the increase of neurological symptoms, and the appearance of paroxysmal disorders of consciousness [5, 7, 12].

In this regard, the development of correction pathogenic action is very important. One of such means is a new anxiolytic Carbatsetam, which is an endogenous modulator of GABA-benzodiazepine receptor complex being a derivative of beta-carboline [1, 3]. It is used as the neuroprotection drug by the positive impact on the brain blood circulation, inhibiting the glutamate excitotoxicity and decreasing the free radical damage by improving the metabolism and energy availability of the neurons [8, 10]. The number of the researches provided the data regarding the anti-inflammatory, anti-tumor, immunomodulation effects [2, 10], the role of the drug in the mechanisms of memory as well as the neuromodulation opportunities in the treatment of Alzheimer's disease [9] and in terms of TBI [8, 12].

Objective of the research. Provide the analysis of the neurologic deficit in dynamics under the experimental traumatic brain injury and methods of its correction by Carbacetam.

Materials and methods of the research. The research was held by means of 140 white outbred male rats, aged six months, weighing 180-220 g, which were kept on a standard diet with free access to food and water in vivarium conditions. TBI modulation was at morning time (from 8.00 to 10.00 am) in the special dedicated ventilated room under the temperature of 18-22 °C, the relative humidity of 40-60% and illumination of 250 lux. The

process was held in compliance with the Helsinki Declaration adopted by the General Assembly of the World Medical Association (2008), the general rules and principles of the European Convention for the Protection of Vertebrate Animals, used for experimental and other scientific aims, as well as the First National Congress on Bioethics and Legislation of Ukraine. The modulation of the traumatic brain injury was based on the method of V.M. Eslki and S.V. Ziablitsev (2005), where the TBI was caused due to gravity load on animals' fixed heads by the strike energy of 0.425 kJ [4]. The rats of experimental group 1 and 2 (n=45 each) were provided Carbacetam (5 mg per 1 kg) and Actovegine (16 mg per 1 kg) during 7 days after TBI [8]. Actovegine was selected for the comparison to Carbacetam effect as the drug being widely used in the treatment of CNS injury (TBI, post-stroke conditions, neuro infections etc.) due to its antihypoxic action, improvement of peripheral blood circulation and tissue trophy [11]. The above-mentioned effects were basis of Actovegine selection for the comparison to Carbacetam. The comparison group consisted of 45 rats were treated by the same manipulations as the above-mentioned experimental groups; however, 1 ml of saline was administered intraperitoneally instead of the experimental medicines. The control group consisted of 5 rats (non-involved), which neurologic symptoms were studied before the TBI as well as under all the terms according to the experimental groups.

The neurologic deficit indicator was estimated under 100-score scale Todd et al. (1981) modified by L.A. Shaliakin (1987), O.Y. Yevtushenko (1989) [4]. Therefore, the following indicators were analyzed in 1 hour followed by TBI: level of consciousness; status of reflex area, including the width and the reaction of pupils to light, corneal reflex, hearing, muscle tone of the body and the reaction to light and pain; breath; movements and some behavioral reactions (tabl. 1).

Table 1

100-score scale Todd et al. (1981) modified by L.A. Shaliakin (1987), O.Y. Yevtushenko (1989) for estimation of the neurologic deficit indicator of the animals [4]

#	INDICATORS	Score	Max.
1	2	3	4
1	**Consciousness level**		
	a) Normal	0	
	b) Blackout or excitement	5	
	c) Stupefaction	10	
	d) Coma	20	20

1	2	3	4
2	**Reflex area**		
	1. Pupil width		
	norm	0	
	narrowed	1	
	widen	2	
	2. Pupil reaction to light		
	present	0	
	weak	2	
	absent	5	
	3. Corneal reflex		
	present	0	
	weak	2	
	absent	5	
	4. Hearing (loud sound reaction)		
	norm	0	
	weak	2	
	absent	5	
	5. Body muscle tone		
	norm	0	
	spastic	2	
	languid	5	
	6. Limb muscle tone		
	a) frontal limbs		
	norm	0	
	spastic	1	
	absent	2	
	б) back limbs		
	norm	0	
	spastic	1	
	absent	2	
	7. Pain reaction		
	present	0	
	weak	1	
	absent	2	28
3	**Breathing**		
	a) Normal	0	
	b) Subnormal or frequent	6	
	c) Absent	12	12
4	**Movements**		
	a) normal coordinated movements	0	
	b) able to walk with minimal ataxia	5	
	c) able to stand, but unable move (stumbles, falls)	10	
	d) unable to stand alone	15	
	e) unable to maintain its position	20	
	f) lack of movement	25	25

1	2	3	4
5	**Behavior and other** 1. Reaction to the appearance of the experimenter a. Responsive b. Unresponsive 2. Able to drink and eat a. capable independently b. able to swallow while infusion c. unable	 0 5 0 2 5	
	1. Personal care a. Active animal, cares about itself in full scope and follows tidiness b. Sad, dull, poor self-care c. Passive animal unfollowing the tidiness	 0 2 5	 15
	TOTAL	100	

The statistical calculations were held by means of Statistica 10 application (StatSoft, Inc, USA).

Research outcomes and their discussion. Administration of ether anesthesia for animals in the control group was accompanied by a blackout of consciousness, pupillary, reduced reflexes and pain threshold, absence of motor responses, slowing breathing. This reaction lasted for 10-15 minutes, followed by 20-30 minutes of full return to consciousness, while the animals demonstrated normal reaction to light and sound, as well as the active grooming. There was not noted any kind of respiratory, motor and behavioral disorders. Assessment of a 100-score scale was 5,4 ± 0,76 points throughout the observation time (from 1st to 30th day of the experiment), which in our view reflects the physiological characteristics of rodents.

Animals of the comparative and experimental groups showed behavioral, motoric and reflex disorders after the provided TBI by the method mentioned above. There were observed the seizures, decrease of the temperature up to 35-36 ºC, reduced heart rate and breathing movements right after the TBI. The brief blackout of consciousness or mild stupefaction that showing the moderate TBI was observed upon the termination of the ether action. The pupils were narrowed, their reaction to light and the corneal reflex was normal or slightly reduced. The hearing response was normal or weakened. The muscle tone of the torso and limbs of most animals was spastic, while reaction to the pain was weakened. The breathing was normal. The animals showed an ability to independent, albeit hindered movement. The behavioral reactions to the appearance of the experimenter, the abilities to drink, to eat, to self- were reduced (see tables 2-4).

Table 2

Neurologic deficit indicators by the areas in ration to the total score by dynamics of the comparative group

Indicator	Day 1	Day 3	Day 7
Consciousness	20,7	19,5	14,6
Reflexes	39,6	42,7	59,6
Breathing	9,8	9,5	0,0
Movements	14,3	13,7	19,7
Behavior	15,6	14,6	6,1

Table 3

Neurologic deficit indicators by the areas in ration to the total score by dynamics of the experimental group 1

Indicator	Day 1	Day 3	Day 7
Consciousness	22,0	22,9* (+3,4 %)	8,6* (-6 %)
Reflexes	40,9	39,2	64,0
Breathing	10,4	9,2	0,0
Movements	15,2	16,1* (+2,4 %)	25,1* (+5,4 %)
Behavior	11,5* (-4,2 %)	12,6* (-2,2 %)	2,3* (-3,8 %)

Note: * – pupils of comparative group are significant under $p < 0,05$

Table 4

Neurologic deficit indicators by the areas in ration to the total score by dynamics of the experimental group 2

Indicator	Day 1	Day 3	Day 7
Consciousness	22,3	20,6** (-2,3 %)	10,2* (-4,4 %) ** (+1,6 %)
Reflexes	41,0	46,0** (+6,8 %)	70,9* (+11,3 %) ** (+6,9 %)
Breathing	10,8	8,3* (-1,2 %) ** (-0,9 %)	0,0
Movements	15,0	13,9** (-2,2 %)	13,8* (-5,9 %) ** (-11,3 %)
Behavior	10,9* (-4,6 %)	11,2* (-3,5 %) ** (-1,3 %)	5,1* (-1,0 %) ** (+2,8 %)

Notes: * – pupils of comparative group are significant under $p < 0,05$

** – pupils of the experimental group 1 are significant under $p < 0,05$

The neurologic deficit (in ration to the total score) of the comparative group animals on Day 1 after TBI was the following according to areas: consciousness – 20.7%; reflexes – 39.6%; breathing – 9.8%; movements – 14.3%; behavior – 15.6%. That means that the major disorders were observed in reflex area. The experimental group 1 had the following indicators: consciousness – 22.0%; reflexes – 40.9%; breathing – 10.4%; movements – 15.2%; behavior – 11.5%. These outcomes did not show the significant discrepancies with the comparative groups but for behavior area being 4.2% ($p < 0,05$) lower than the indicator of the comparative group. The experimental group 2 had the following neurologic symptoms on Day 1 after TBI: consciousness – 22.3%; reflexes – 41.0%; breathing – 10.8%; movements – 15.0%; behavior – 10.9%. These outcomes do show the significant discrepancies with the comparative group and the experimental group 1 as well but for behavior area being 4.2% ($p < 0,05$) lower than the indicator of the comparative group.

Day 3 after TBI showed the following changes of the neurologic symptoms: consciousness – 19.5%; reflexes – 42.7%; breathing – 9.5%; movements – 13.7%; behavior – 14.6%. The experimental group 1 had the following indicators: consciousness – 22.9%; reflexes – 39.2%; breathing – 9.2%; movements – 16.1%; behavior – 12.6%. These outcomes showed the significant discrepancies with the comparative group ($p < 0,05$) for consciousness (+3.4%), movements (+2.4%) and behavior (-2.2%). The experimental group 2 had the following neurologic symptoms on Day 3 after TBI: consciousness – 20.6%; reflexes – 46.0%; breathing – 8.3%; movements – 13.9%; behavior – 11.2%. These outcomes showed the significant discrepancies ($p < 0,05$) for consciousness (-2.3%) with experimental group 1, reflexes (+6.8%) with experimental group 1, breathing with comparative group and with experimental group 1 (-1.2% and -0.9% accordingly), movements with experimental group 1 (-2.2%) and behavioral reactions with comparative group and with experimental group 1 (-3.5% and -1.3% accordingly).

Day 7 showed the following changes for the comparative group: consciousness – 14.6%; reflexes – 59.6%; breathing – 0.0%; movements – 19.7% and behavior – 6.1%. The experimental group 1 had the following indicators: consciousness – 8.6%; reflexes – 64.0%; breathing – 0.0%; movements – 25.1%; behavior – 2.3%. These outcomes showed the significant discrepancies with the comparative group ($p < 0,05$) for consciousness (-6.0%), movements (+5.4%) and behavior (-3.8%). The experimental group 2 had the following neurologic symptoms on Day 7 after TBI: consciousness – 10.2%; reflexes – 70.9%; breathing – 0.0%; movements – 13.8%; behavior – 5.1%. These outcomes showed the significant discrepancies ($p < 0,05$): for consciousness with the comparative group and

experimental group 1 (-4.4% and +1.6% accordingly); reflexes with the comparative group and experimental group 1 (+11.3% and +6.9% accordingly); movements with the comparative group and experimental group 1 (-5.9% and -11.3% accordingly); and behavioral reactions with comparative group and with experimental group 1 (-1.0% and +2.8% accordingly).

Conclusions. The data received indicated the mild albeit significant recovery of the neurologic symptoms of the rats under Carbacetam impact on 3rd and 7th day of the treatment onto reflexes, behavior and consciousness. Actovegine has had major effect in comparison to Carbacetam action in motoric area. This may be applied under the development of the appropriate guidelines for the treatment and rehabilitation of the patients suffering the TBI depending on the major neurologic disorders.

Further research and development perspectives. It is planned to study the impact of Carbacetam and Actovegine onto the cognitive functions of the rats.

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