Melatoninergic antidepressants in the treatment of post-stroke depression

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Abstract. The article presents data about the impact of the drug Melitor (agomelatine) on the psycho-emotional activity, cerebral hemodynamics, bioelectric activity of the brain and their intersystem connections in patients with post-stroke depression. 30 patients with post-stroke depression have been taken a dose of Melitor 25 mg per day for 2 months. It has been established that Melitor has a positive effect on psycho-emotional activity, improves cerebral hemodynamics, harmonizes the structure of bioelectric activity of the brain in patients with post-stroke depression. Melitor has more strong effect on cerebral hemodynamics and bioelectric activity of the brain in patients with right-sided stroke than among the patients with left-sided stroke. Melitor's multimodal influence justifies the use of the drug during the rehabilitation treatment of post-stroke patients for the improvement both functional and psycho-emotional state.

Keywords: ischemic stroke, post-stroke depression, cerebral hemodynamics, bioelectric activity of the brain, Melitor

The large frequency range of post-stroke depression is conditioned by the methodological differences of the criteria for the diagnosis of depression and the time of the start concerning to the beginning of a stroke. Rehabilitation of the patients who have had a stroke is an important medical and social problem. A stroke leads to malfunction of motor, sensitive, psycho-emotional sphere, narrows the range of social and everyday activities. It requires a long and systematic rehabilitation to restore walking, self-care of household skills, statics [1, 2]. The factors that negatively influence the rehabilitation of patients with stroke are changes in the psycho-emotional sphere: depression and dementia [3, 4]. One of the main mechanisms of the negative impact of depressive disorders on the effectiveness of the rehabilitation treatment is a decrease of the patient's motivation to participate in rehabilitation activities [5, 6].

The prevalence of post-stroke depression ranges from 5 up to 67%. 18-55% of stroke survivors suffer from depression in 2 years after stroke. Women are more prone to the vascular depression, the peak is observed during the first 3-6 months after stroke, but the risk of the appearance of depression remains still high for the first two years [7, 8]. The risk factors for the post-stroke depression are considered to be age, the presence of subcortical atrophy before stroke, family and personal anamnesis, with the reference to the psychiatric disorders in past [9, 10]. The question about the influence of hemispheric localization of the stroke on the frequency of depression is rather contradictory. Some people consider that the hemispherical localization of a stroke does not matter, others note that the frequency and complication of post-stroke depression is higher when the left hemisphere is affected [11]. A post-stroke depression has been found to be highly correlated with cognitive impairments, with a passive perception of quality of life and increased mortality. It has been shown that in patients who have had a stroke within 15 months of rehabilitation, patients with depression died 8 times more often than the patients without depression [12, 13, 14]. According to transcranial dopleography there is a decrease of the rate of cerebral blood flow in patients with post-stroke depression [15].

That is why adequate treatment of post-stroke depression should be considered not only as an opportunity to reduce the severity of depressive symptoms, but also as a way to improve the quality of life, increase the efficiency of rehabilitation and reduce the severity of physical disorders in after-stroke patients [16, 17]. During the last years, it has been noted that certain groups of antidepressants, when used in the acute stroke, increase brain plasticity and thus contribute to the maximal neurological recovery after stroke.

Drug treatment of depression is considered to be one of the components of the rehabilitation process for post-stroke patients [18]. Prescription of the antidepressants is the main method of modern treatment of depression [19]. Improvement of the approaches to the treatment of post-stroke depression occurs in accordance with the development of pathogenetic mechanisms of depression and energy depletion of cortical biogenic amines, especially expressed in a case of lesion of the left frontal area and basal ganglia [24]. Serotonin selective reuptake inhibitors (SSRIs) are most commonly used in the treatment of post-stroke depression. This class of antidepressants causes less cases of side effects than tricyclic antidepressants, which often lead to cardiotoxic reactions. However, the use of SSRIs is also limited due to the presence of a population of patients with cerebrovascular pathology refractory to SSRI therapy [16, 19].

The first choice drugs in the treatment of post-stroke depression for the aged people are the new generation antidepressants, in particular melatonergic antidepressants [21]. Agomelatine (Drug "Melitor®" production by Servier) is a representative of this class. "Melitor" is an antidepressant capable to restore circadian rhythms that are broken among the patients with depression. "Melitor" is an MT-1 and MT-2 agonist of melatonin receptors and an antagonist of serotonin 5-HT_{2c} receptors, which are located in the suprachiasmatic nucleus that is responsible for the regulation of circadian rhythms [22]. The influence of "Melitor" on these three types of receptors provides an expressed antidepressant and anxiolytic effect. The medical effect of "Melitor" is already observed by the end of the 1st week of therapy, when the patient's daily rhythm is normalized, his daily activity and sleep quality are improved, during the 2-3 weeks of taking of the drug, the mood and the cognitive functions are improved [6, 21, 23, 24].

Purpose

Comprehensive analysis of the effect of "Melitor" on the functional status of the CNS in patients with ischemic stroke with post-stroke depression.

Materials and methods

30 aged patients took the drug in a dose of 25 mg 1 time per day in the evening during 2 months. A comprehensive examination was held before and after taking "Melitor", including neuropsychological studies (gerontological depression scale, Hamilton scale), assessment of social and household activity level (Bartel index), analysis of the state of cerebral hemodynamics (EnVisor device, PHILIPS) and bioelectric activity of the brain ("Neurofax EEG - 1100K", NIHON KOHDEN). The statistical data processing applied software "Statistica® for Windows 6.0" was used to process the received information. The correlation connections between the indicators of cerebral hemodynamics and the intensity of the main rhythms of EEG was established by determining the correlation coefficient, while taking into account statistically significant strong correlation connections ($r > 0.70$).

Results and their discussion

Analysis of the dynamics of subjective complaints from patients who suffered from ischemic stroke with depression before and after a 2-month course of "Melitor" showed that the drug reduces the number and intensity of complaints from the patients (Tab. 1)

Table 1

Dynamics of subjective complaints in patients after ischemic stroke, before and after the course of Melitor, %

Complaints	Patients with localization of the ischemic focus in the right hemisphere		Patients with localization of the ischemic focus in the left hemisphere	
	Before treatment	After treatment	Before treatment	After treatment
Headache	46.7	16.7	43.3	20.0
Bad dream	40.0	20.0	40.0	16.7
Internal tension	43.3	26.7	40.0	23.3
Impaired appetite	50.0	16.7	46.7	20.0
Impaired attention	50.0	20.0	43.3	23.3
Physical fatiguability during the physical therapy	50.0	20.0	46.7	16.7

So, 2 months after taking “Melitor”, patients with right- and left-hemisphere stroke, have sleep improvement, decrease of fatiguability during physical exercises, reduction of headaches and irritability.

The level of depression and anxiety among the patients who have had a stroke, statistically significantly decreases under the influence of the “Melitor” (Tab. 2).

Table 2

The dynamics of the indicators of the Hamilton depression scale and Gerontological scale among the patients after ischemic stroke, before and after the course of “Melitor”, points

Scales	Patients with localization of the ischemic focus in the right hemisphere		Patients with localization of the ischemic focus in the left hemisphere	
	Before treatment	After treatment	Before treatment	After treatment
Gerontological	15.1±1.3	7.1±1.8*	11.2±1.2	4.3±1.2*
Hamilton	21.0±1.5	8.2±1.05*	19.0±1.2	7.4±1.0*

Notes: * - statistically significant differences between the indicators before and after treatment

According to the Gerontological scale of depression, “Melitor” induces a few more expressed decrease of the level of depression in patients with right-hemispheric stroke than in patients with left-hemisphere localization of stroke. The patients with left hemisphere stroke have statistically significant lower indicators of constitutional anxiety in accordance to the Spielberg-Khanin scale (before treatment, 46.7 ± 2.1 after 38.1 ± 1.8 points) and reactive anxiety rates (respectively, from 44.6 ± 2.2 up to 34.2 ± 1.1 points). “Melitor” also reduces the level of constitutional (from 51.5 ± 2.0 to 41.4 ± 2.31 points) and reactive (from 47.1 ± 1.8 to $37.0 \pm 3, 1$ points) anxiety among the patients with localization of the stroke in the right hemisphere,.

Thus, “Melitor” has an anxiolytic effect in patients who have suffered from an ischemic stroke: it reduces anxiety symptoms in the framework of depressive disorders. Patients have statistically confirmed significantly reduced level of both mental and somatic components of anxiety.

In patients who have had a stroke, under the influence of taking “Melitor”, the level of social and household activity increases in accordance with the Bartell scale from 78.3 ± 2.4 to 91.5 ± 1.8 points, clinically this is confirmed by an increasing of motor activity and an extension of the range of domestic self-service, improvement of the coordination.

To analyze the mechanisms that determine the effect of “Melitor” on the psycho-emotional state of patients who have suffered from an ischemic stroke, the analysis of the functional state of the brain was made (the indicators of cerebral circulation and bioelectrical activity of the brain were taken into account) before and after the course of “Melitor” treatment. “Melitor” improves cerebral hemodynamics, in patients who have had a stroke, because LSBV is statistically significantly increased in some vessels of the carotid and vertebro-basilar pools.

However, it should be noted that the effect of the drug on high-speed indicators of cerebral blood flow has hemispheric peculiarities (Tab. 3). In patients who had an ischemic stroke with localization of the ischemic focus in the right hemisphere, LSBV in the right MBA, left ICA, in two VA, two CA and BA is statistically significantly increased. In left hemisphere patients, under the influence of taking of “Melitor”, LSBV is statistically significantly increased only in BA.

Table 3

The dynamics of the linear systolic blood flow speed in patients after ischemic stroke, under the influence of the taking a course of the drug “Melitor”, cm / s

Vessels		Patients with localization of the ischemic focus in the right hemisphere		Patients with localization of the ischemic focus in the left hemisphere	
		Before treatment	After treatment	Before treatment	After treatment
CCA	Affected	61.9 ± 4.3	64.2 ± 4.5	74.5 ± 4.5	72.1 ± 3.2
	Intact	75.0 ± 5.2	73.1 ± 5.5	66.3 ± 5.6	69.9 ± 4.6
ICA	Affected	75.5 ± 2.5	70.7 ± 2.3	72.2 ± 7.6	73.7 ± 5.5
	Intact	61.9 ± 1.7	$70.8 \pm 2.2^*$	63.8 ± 2.8	65.6 ± 2.6
VA	Affected	36.1 ± 1.5	$42.7 \pm 1.9^*$	44.1 ± 2.2	44.9 ± 2.3
	Intact	38.2 ± 1.9	$45.7 \pm 2.3^*$	39.8 ± 1.1	42.5 ± 2.1
CA	Affected	80.8 ± 2.2	$87.0 \pm 2.5^*$	94.6 ± 4.7	95.2 ± 5.3
	Intact	75.2 ± 2.0	$87.7 \pm 2.1^*$	94.2 ± 5.7	88.4 ± 4.9
MBA	Affected	87.9 ± 4.1	$103.7 \pm 4.5^*$	92.7 ± 5.2	94.5 ± 5.5
	Intact	106.0 ± 4.8	104.9 ± 3.5	107.0 ± 4.1	107.9 ± 6.4
PCA	Affected	46.4 ± 1.4	$52.7 \pm 2.9^*$	52.5 ± 2.2	52.8 ± 3.1
	Intact	49.0 ± 1.3	53.7 ± 3.1	54.6 ± 2.1	54.6 ± 2.3
BA		53.2 ± 2.4	$61.0 \pm 3.4^*$	54.1 ± 3.1	$61.9 \pm 2.5^*$

Notes: * - statistically significant differences between the indicators before and after treatment

In patients with ischemic stroke, the course of the drug “Melitor” decreases the indices of peripheral resistance, predominantly among the patients with localization of the focus in the left hemisphere. Thus, in right hemisphere patients, under the influence of “Melitor”, the pulsatory index in the intact RMA is statistically significantly reduced (before treatment 0.8 ± 0.05 , after - 0.7 ± 0.02), whereas in left hemisphere patients the pulsator index in the affected ICA decreases (0.9 ± 0.04 and 0.8 ± 0.03 , respectively) and intact CA (0.8 ± 0.02 and 0.7 ± 0.03), as well as the index of circulatory resistance in the affected CA (before treatment - 0.5 ± 0.02 , after 0.4 ± 0.03), which indicates a bit more expressed positive effect of “Melitor” on the indices of peripheral resistance in patients after stroke with localization of the focus in the left hemisphere.

Taking into account that computer EEG allows to quantify the degree and the structure of functional changes of the brain and their dynamics, which can serve as an objective criterion for the evaluation of mechanisms of drugs influence on the patients with stroke, the analysis of brain bioelectric activity in patients with post-stroke depression under the influence of taking a course of “Melitor”. It is established that

the structure of reorganization of intensity of the main rhythms of EEG under the influence of “Melitor” in patients who have had a stroke has certain hemispherical peculiarities.

In patients with right-sided stroke, “Melitor” reduces in all areas of the two hemispheres the intensity in the delta range (maximum in the frontal area of the affected hemisphere: before treatment 1.2 ± 0.01 , after $0.8 \pm 0.07 \mu\text{V}$) and theta rhythm (maximum in the central region of the affected hemisphere: before treatment 1.2 ± 0.01 , after $-0.9 \pm 0.01 \mu\text{V}$) against the background of increasing intensity of alpha-1 rhythm (maximum in the central region of the affected hemisphere: 0.9 ± 0.02 and $1.6 \pm 0.03 \mu\text{V}$, respectively) and alpha rhythm frequency (maximum in the central region of the intact hemisphere: before treatment 9.8 ± 0.03 , after $-10.5 \pm 0.02 \text{ Hz}$) - see Figure 1.

The patients with left-hemispheric stroke under the influence of “Melitor” statistically significantly have increasing of the intensity only in the alpha-1 range (maximum in the frontal area of the intact hemisphere: before treatment 1.1 ± 0.01 , after $-1.5 \pm 0.01 \mu\text{V}$) and alpha-2 rhythms (maximum of the central region of the affected hemisphere: 0.6 ± 0.01 and $1.5 \pm 0.04 \mu\text{V}$, respectively) in the two hemispheres (Fig. 1).

Figure 1. Statistically significant changes in the intensity of major EEG rhythms among the patients with ischemic stroke with the localization of the focus in the right (A) and left (B) hemispheres under the influence of “Melitor”

Under the influence of “Melitor” patients with post-stroke depression, have reorganization and intersystem relationships between cerebral hemodynamics and the structure of bioelectric activity of the brain. The type of reorganization has expressed hemispherical peculiarities.

The structure of correlation relationships between the intensity of the main EEG rhythms and the indicators of cerebral blood flow before and after taking of the drug “Melitor” of the patients with right-sided stroke is quantitatively and qualitatively different from the structure of correlation connections of the patients with left-sided stroke.

In patients with depression with right-sided stroke, “Melitor” increases the number of correlation relationships between linear blood flow speed in VA, ICA, CCA, and intensity in the range of delta and theta rhythms from 3 to 9 and between the intensity in the alpha-1 and alpha-2 range from 3 up to 11 (Fig. 2A).

Figure 2. Structure of the changes in statistically significant strong correlation ($r \geq 0.7$) between LSBV in vessels of carotid and vertebro-basilar basins and intensity of main EEG rhythms among the patients with post-stroke depression with left-hemispheric (B) and right-hemispheric (A) stroke under the influence of “Melitor”

The range of the relationships of the intensity of the main EEG rhythms with the indicators of cerebral hemodynamics, contracts in patients with depression with left-hemispheric stroke. Before taking “Melitor”, there are 7 statistically significant correlation relationships between the intensity of slow rhythms (delta, theta-) and LSBV in vessels of the carotid pool (ICA and VA), after the taking the drug there are only two

(between LSBV in BA and CCA) statistically significant correlations. In patients with left-hemispheric stroke, the background number of correlation relationships between intensity in the range of alpha-1 and alpha-2 rhythms with LSBV in vessels of the carotid and vertebro-basilar pools is 16, and the connections after the taking of "Melitor" are leveled. Only are noted between the intensity of alpha-1 and LSBV in BA and RMA. Hemispheric peculiarities of the effect of "Melitor" on the structure of relationships between indicators of brain bioelectric activity and blood flow speed in some vessels of the carotid and vertebro-basilar pools in patients with post-stroke depression are due to functional-biochemical asymmetry of the brain [25].

Thus, the patients with ischemic stroke, under the influence of "Melitor", have the reduction of the level of anxiety and depression, the extension of the range of functional activity, improvement of the cerebral hemodynamics and functional-metabolic processes in the structures that generate bioelectric activity of the brain, and indicators of bioelectric activity of the brain. More expressed influence of "Melitor" on psycho-emotional activity, cerebral hemodynamics and bioelectric activity of the brain was obtained in patients with post-stroke depression with the localization of the ischemic focus in the right hemisphere.

Conclusions

Based on the foresaid, we can make the following conclusions:

1. In patients who have had a stroke, a course of taking (2 months) of "Melitor" in a dose of 25 mg per day, improves overall well-being, sleep, reduces the frequency and intensity of headaches, reduces the level of anxiety and depression, extends the range of social and household activity.
2. The effect of "Melitor" on the bioelectric activity of the brain in patients with atherothrombotic stroke in the right and left hemispheres is characterized by a decrease in the intensity in the range of slow rhythms against the background of increased intensity and frequency of alpha rhythm.
3. "Melitor" improves cerebral hemodynamics in patients with ischemic stroke. In a case of localization of the ischemic focus in the right hemisphere we observe the increase of the speed indicators of cerebral circulation in some vessels of carotid (MBA, CA, ICA) and vertebro-basilar (VA) pools. Patients with left-hemispheric stroke under the influence of "Melitor" have statistically significantly increase LSBV only in VB (BMA) vessels.
4. In patients with localization of the ischemic focus in the right hemisphere, the effect of "Melitor" on cerebral hemodynamics and bioelectric activity of the brain is more expressed than in patients with left-hemispheric stroke.
5. Under the influence of course taking of "Melitor" in patients with ischemic stroke in the left hemisphere 7 times decreases the range of correlation relationships between LSBV and the intensity of individual EEG rhythms, in patients with right-hemispheric stroke it increases 4 times, which indicates the hemispheric peculiarities of reorganization of connections between the hemodynamics and bioelectric activity of the brain in patients with ischemic stroke due to functional-biochemical asymmetry of the brain.

Abbreviations

LSBV - linear systolic blood flow velocity,
 MT-1, MT-2 - melatonin receptors,
 MBA - midbrain artery,
 ICA - internal carotid artery,
 VA - vertebral artery,
 CA - cerebral artery,
 BA - basilar artery,
 CCA - common carotid artery,
 PCA - posterior cerebral artery,
 VB - vertebrobasilar basin,
 BMA – basic main artery.

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