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Rivastigmine in the Treatment of Dementia: From the Symptomatic Effect to Neuroprotection

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ABSTRACT

Dementia is a hot topic today, largely as a result of the ageing of the population. One of the most common causes of dementia is Alzheimer's disease (AD). This disease, which is classified as a primary degenerative dementia, is characterized by a progressive decline in cognitive functions, primarily memory, and the development of behavioral disorders.

Introduction. There are estimated to be about 24 million patients with AD worldwide, and this number is expected to triple over the next 3-4 decades. However, dementia is not only an important medical problem, but also a major socioeconomic burden for the patient, caregivers, family members and society at large. AD, in particular, is one of the leading causes of disability in highly developed countries, and caring for a patient with AD drastically reduces the quality of life of the caregivers themselves.

Central acetylcholinesterase inhibitors, which are considered first-line therapy, are now widely used in the treatment of AD.Improvement in the condition of patients with this group of drugs is observed in 40-80% of cases. The rationale for their use in AD is the presence of central acetyl cholinergic deficiency, which is one of the key pathogenetic mechanisms of this disease. There is a correlation between the severity of dementia and central cholinergic deficits. The degree of cholinergic deficit in the cortex is closely related to a decrease in the number of neurons in the basal areas of the brain, particularly in the basal Meinert's nucleus, where acetylcholine-producing neurons are located. In addition, there is a decrease in the number of cholinergic receptors in the cortex.

Acetylcholine is produced in presynaptic terminals by acetylcholine transferase, and then it accumulates in vesicles, in which it is transported to the presynaptic membrane. After release of acetylcholine into the synaptic cleft, it acts on postsynaptic cholinergic receptors. Acetylcholine is degraded by acetylcholinesterase, an enzyme present in both presynaptic and postsynaptic membrane regions. It has now been shown that, in addition to acetylcholinesterase, acetylcholine levels in the brain are regulated by another enzyme, butyryl cholinesterase. Therefore, a double-acting drug, i.e., one capable of inhibiting both acetylcholinesterase and buty rylcholin esterase,

would be expected to have a greater effect. Butyrylcholinesterase is found in senile plaques, fibrillary glomeruli and in the vascular wall (in amyloid angiopathy). This enzyme is thought to be involved in the formation of senile plaques. It is assumed that butyrylcholinesterase activity is most pronounced in the subcortical white matter of the brain, and increased activity of this enzyme in these areas explains the increase in the severity of cerebral atrophy and ventricular system size during the progression of cognitive impairment in dementia patients. It should be noted that the most significant increase in butyrylcholinesterase activity during aging is observed in the areas of white matter that melanized later in normal child development, in particular in the entorhinal areas.

Experimental and clinical studies suggest that inhibition of butyrylcholinesterase is associated with improved learning ability, memory, and visual-spatial function. It has been shown that as AD progresses, the activity of acetylcholinesterase in certain areas of the brain decreases, while the activity of butyrylcholinesterase increases. Given this fact, it is preferable to prescribe drugs capable of inhibiting both acetylcholinesterase and butyrylcholinesterase - inhibition of acetylcholinesterase alone may not be sufficient to achieve the required therapeutic effect. Rivastigmine is precisely this dual mechanism of action.

Rivastigmine (Exelon, Novartis Pharma, Switzerland) is a slow reversible acetylcholinesterase and butyrylcholinesterase inhibitor, mainly acting centrally. It is used for the treatment of mild to moderate dementia in AD and Parkinson's disease. Against the background of its administration, there is a rapid dose- dependent inhibition of these enzymes in the cerebrospinal fluid of AD patients. A significant inhibition of acetylcholinesterase activity was observed after a single dose of 3 mg of rivastigmine. The drug acts predominantly on hippocampal, temporal and frontal lobe structures; its effects on cerebral structures persist for up to 10 h.

The efficacy of rivastigmine has been evaluated in a large number of studies from different countries. During therapy, the most significant clinical improvement is observed from week 12 from the start of therapy, with a dose-dependent efficacy. In addition to improved cognitive function, the therapy also reduces the severity of self-care disorders, which is of great importance for the relatives of the patients. Rivastigmine has been shown to be highly effective in patients whose AD is complicated by hallucinations. It is important to note that the effectiveness of rivastigmine is maintained for a long time.

The drug is characterized by its selective action, as it predominantly inhibits the G1-isoform of acetylcholinesterase (it is expressed to a greater extent in the hippocampus and cortex, i.e. in the areas primarily affected by AD) and to a lesser extent the G4-isoform, which results in a significant decrease in the probability of peripheral adverse events. The selective effect of rivastigmine on the G1-isoform of acetylcholinesterase is thought to explain the rare occurrence of extrapyramidal adverse reactions. The same property of rivastigmine explains the rare occurrence of muscular crumpets that is characteristic of other acetylcholinesterase inhibitors. It should be noted that the genesis of crania on therapy with acetylcholinesterase inhibitors is related to the effect on the G2-isoform of the enzyme, located predominantly in the neuromuscular terminals. The selectivity of rivastigmine, as well as its dual effects, make it preferable to prescribe not only in the early but also in the advanced stages of AD.

It should be noted that the use of acetylcholinesterase inhibitors in clinical practice is often associated with the development of cholinergic-induced headache, nausea, dizziness and diarrhea, which are typical of this class. They are usually mild to moderate in severity, limited in duration and not life-threatening.

This necessitates the development of new approaches, in particular the introduction of new means of delivery acetylcholinesterase inhibitors characterized by the absence of concentration peaks, a decrease in the frequency of adverse events and, as a result, an increase efficiency due

to the greater likelihood of achieving optimal dose.

The use of the drug is not only a means of reducing adverse events, but also increases efficacy by making it more likely that the optimal dose will be achieved.

More recently, a new form of rivastigmine in patch form (transdermal therapeutic system) has been introduced into clinical practice. This form of rivastigmine has undoubted advantages over the conventional oral form of the drug, due to the ability to continuously deliver rivastigmine into the bloodstream within 24 h. This is mainly due to the absence of fluctuations in serum concentrations when used as a patch, which results in a 3-fold reduction in the incidence of side effects - with high clinical efficacy and greater patient compliance. In the vast majority of cases, no local irritant effect is observed with the patch.

The literature suggests that rivastigmine has a good combination of good efficacy and tolerability. The studies conducted to date have mainly included elderly and elderly patients, who usually have concomitant somatic pathology. It should be noted that polymorbidity is very common in elderly and elderly patients, with an average of more than 3 diseases in persons over 65 years of age, so that elderly patients take more than 3 medications (especially often cardiovascular, analgesics and sleeping pills).

Studies have shown that rivastigmine is well tolerated in this population. It can be combined with a wide range of drugs commonly used in neurogeriatric practice, including antipsychotics. No adverse effects on electrocardiographic parameters have been reported .

In practice, it is often necessary to switch from one acetylcholinesterase inhibitor to another. Such problems, either due to insufficient efficacy or to the development of side-effects, occur in mild to moderate AD in almost 50% of cases. It has been shown that patients who do not benefit from other central acetylcholinesterase inhibitors may improve with rivastigmine. Moreover, unlike other acetylcholinesterase inhibitors, rivastigmine has a low potential for interaction with other indications, which is particularly important for elderly patients.

The neuroprotective effect of rivastigmine

Studies have reported improvement with central acetylcholinesterase inhibitors, including rivastigmine, not only in mild to moderate but also in severe dementia. However, the need for the earliest possible initiation of this group of drugs is emphasized, which is thought to delay disease progression. According to some authors, positive dynamics in the state patients on the background of therapy with acetylcholinesterase inhibitors is manifested not only in improving the results performing neuropsychological tests, but more slow progression of the disease.

Until recently, there was no strong evidence of a protective effect of this group of drugs in AD, which may be due in large part to the design of the trials, which were mostly short-lived. The situation has changed recently. Even after withdrawal of acetylcholine esterase inhibitors, the degree of progression of the pathological process has been shown to decrease, and clinically this is manifested by a slower increase in cognitive and behavioral disorders. The suggestion that acetylcholinesterase inhibitors, particularly rivastigmine, have a protective effect is supported by long-term follow-up of patients with moderate cognitive impairment (MCI) over 3-4 years – receiving this therapy. It should be noted that RBM is often seen as a prodromal stage of AD, and the risk of developing the disease is significantly higher in women with RBM than in men.

The concept of RBM has been proposed to refer to pre- diagnostic disorders of higher brain functions caused mainly by AD. AD progresses through a series of stages characterized by a progressive increase in symptomatology, from mild cognitive impairment, primarily in memory, to severe impairment reaching the degree of dementia. The duration of the prodromal (preclinical) phase of the disease is unknown, but there is no doubt that it lasts for years. The

term SCD has been coined to describe this prodromal period. However, there is no clear distinction between normal ageing and AD and between AD and AD (its early stages). Theoretically and practically, patients with UCD are an important group. From a theoretical point of view, the study of these disorders allows us to get closer to understanding the clinical features of the earliest manifestations of dementia (mainly AD) and is also important in the context of the "neurology of normal aging". From a practical point of view, the identification of those with mild cognitive impairment at the time of examination, but who are at risk of developing dementia, allows the use of certain therapeutic programmers at the earliest stages of the disease. It is in this category of patients that their effectiveness can be expected to be greater. In addition, the efficacy of neuroprotective therapies, which are currently under development, is more reasonable and promising.

The prevalence of UCD is as high as 10% in those over 65 years of age, and 10-15% of them develop a full clinical picture of AD within a year. Some caution should be exercised in treating UCD as a key early stage of AD, as other causes, including depression, cerebrovascular lesions, frontotemporal dementia, diffuse Levi's disease, etc., may also underlie them. Currently some cases of MCD are considered as a preclinical stage of vascular dementia. There are at least two variants of vascular dementia. In the first of them, with marked diffuse changes in the white matter of the cerebral hemispheres, the clinical picture is dominated by executive function disorders, while the second is associated with infarcts and repeated episodes of acute circulatory disturbances and is manifested by more polymorphic symptoms, the nature of which is determined by the localization of the ischemic focus(s).

Rivastigmine administration in UCD is not only associated with a positive clinical effect, but also reduces the risk of AD in this category of patients, although the absence of such an effect was previously reported. It should be noted that the positive effect is related to the gender of the patients - a significant reduction in the risk of AD in patients with UCP was observed in women, while in men this effect was not statistically significant. In addition, women with amnestic type of ALS who receive rivastigmine for a long time showed a decrease in the degree of cerebral atrophy and ventricular volume increase compared to patients receiving placebo. It has now been shown that the efficacy of the drug is to some extent determined by the available butyrylcholinesterase genotype. When considering the results showing differences in the efficacy of rivastigmine in men and women, certain features of the white matter structure depending on gender, at least as indicated by magnetic resonance imaging, should also be considered.

Cortical atrophy in parieto-temporal regions is less significantly increased in patients with AD receiving rivastigmine compared to the group of patients receiving placebo or other selective acetylcholinesterase inhibitors. Against the background of rivastigmine therapy, white matter volume decreases less significantly than that of other acetylcholinesterase inhibitors, including in deep parts of the hemispheres and brainstem. Many researchers believe that the protective effect of rivastigmine, the ability of this drug to decrease progressing white matter atrophy and, correspondingly, to keep intact cortical- subcortical connections, is caused mainly by butyrylcholinesterase inhibition. It is emphasized that the neuroprotective effect is based on the blocking of butyrylcholinesterase outside synapses, in glial tissue, in deep parts of cortical and subcortical structures, which, in particular, leads to a decrease in the proinflammatory effect of this enzyme.

Recently, anti-inflammatory effect has been shown to be one of the mechanisms of action of this drug, leading to the reduction of amyloid deposition. In particular, the ability of rivastigmine to reduce demyelination, microglia activation, proinflammatory cytokine formation and axonal damage was demonstrated in the model of experimental autoimmune encephalomyelitis. The role of inflammatory processes in the pathogenesis of AD is now emphasized. The data obtained

indicate the importance of the non-synaptic mechanism of action of acetylcholinesterase inhibitors on the progression of AD, associated with the influence of this group of drugs on the processes of myelination in central nervous system.

Prospects for rivastigmine in other dementias

The efficacy of acetylcholinesterase inhibitors, particularly rivastigmine, has been noted not only in AD and dementia sodica, but also in other forms of dementia - dementia with Levy corpuscles, dementia due to Parkinson's disease and dementia due to craniocerebral trauma (CST).

It is important to note that in addition to the direct restoration of the acetyl cholinergic defect, central acetylcholinesterase inhibitors can also affect cerebral blood flow. In AD, according to functional neuroimaging methods, there is a decrease in regional cerebral blood flow and metabolism, which is most pronounced in the temporoparietal and frontal regions. The localization of the hypometabolic zones does not always coincide with the areas with the characteristic acetyl cholinergic defect. However, low regional blood flow in the temporal regions is one of the predictors of rapid progression of cognitive defect.

It has been suggested that central acetylcholinesterase inhibitors can improve cerebral perfusion, and thus, this group of drugs can be effective in cases of both vascular and primary degenerative genesis of dementia. In fact, the treatment with central acetylcholinesterase inhibitors in patients with AD is associated with an increase in regional cerebral blood flow.

In particular, rivastigmine not only increases cerebral acetylcholine levels, which are decreased due to the disease, but also increases cerebral blood flow in the frontal, parietal and temporal regions, which is accompanied by an improvement in the cognitive performance of patients. However, it is possible that these changes in blood flow are not related to the effect of rivastigmine directly on vessels, but rather to the increased metabolism in the areas of the brain where acetyl choline responsive neurons are preserved (stimulation of neuronal activity at postsynaptic level).

Acetyl cholinesterase inhibitors (galantamine, rivastigmine, donepezil) are now shown to be effective not only in AD, but also in vascular dementia. Cognitive and behavioral improvement was observed in patients with subcortical vascular dementia who received rivastigmine for 52 weeks. It is possible that some of the cases included in these studies were not patients with 'pure' vascular dementia, but with mixed dementia. It should be noted that there is very limited evidence that a cholinergic defect is not characteristic of "pure" sodic dementia (i.e., without coexisting alzheimer changes). However, the concept of an acetyl cholinergic defect in vascular dementia is supported not only by clinical, but also by experimental and pathomorphological data. In particular, in a specially bred line of rats with a hereditary predisposition to arterial hypertension and strokes (experimental model of vascular dementia), a significant decrease in acetylcholine and choline is observed in cerebral cortex, hippocampus and spinal cord liquids. According to autopsy data, patients with vascular dementia show cholinergic deficits in the cortex, hippocampus and striatum, as well as decreased acetylcholine concentration in the cerebrospinal fluid postmortem.

It is important to emphasize that subcortical vascular foci can lead to central acetyl cholinergic deficits even in the absence of concomitant Alzheimer's changes [8, 52]. Central cholinergic structures, the preservation of which is extremely important in cognitive function, are affected by ischemia, and hippocampal atrophy can be detected in patients with vascular dementia in the absence of comorbid AD.

It should be noted that 'pure' vascular dementia is rare in practice. In the elderly and elderly, there is usually a combination of vascular and primary degenerative (Alzheimer's) changes. Such

cases are more appropriately considered as mixed dementia. It is now emphasized that the use of central acetylcholinesterase inhibitors in mixed dementia is as effective as in AD.

Traumatic brain injury is the 3rd most common cause of dementia (after infectious diseases and alcoholism) in people under 50 years of age. In developed countries, motor vehicle accidents are responsible for about 50% of all traumatic brain injuries, but in the elderly and elderly, falls are more likely to cause traumatic brain injuries. Men are more likely than women to suffer a traumatic event. The severity of cognitive impairment after a traumatic event depends on a number of factors, including the nature and severity of the injury, age of the patient, location of the lesion and premorbid cognitive level. In general, dementia may occur in approximately 3-10% of patients who survive severe trauma.

The progression of cognitive impairment after trauma may be based on acetyl cholinergic disorders similar to those in AD, blood-brain barrier disorders, autoimmune and vascular disorders due to trauma, and the development of hydrocephalus. It should be noted that trauma increases the risk of AD, and pathomorphological examination of the brain of trauma victims often reveals changes characteristic of AD [7, 9]. In this regard, there is interesting evidence that the cerebral inflammatory reactions in AD and trauma are similar [33]. The brain is shielded from the immune system by the blood-brain barrier, which is normally only invaded by peripherally activated T cells. In a traumatic brain injury, proinflammatory cytokines, interleukin-1β and tumor necrosis factor cause increased β - amyloid formation. This may eventually lead to the neuronal degeneration characteristic of AD.

Since in all types of dementia, cognitive deficits are often associated with impaired executive functions and are caused by disconnection of the forebrain with cortical and subcortical structures, rivastigmine has certain advantages due to its dual mechanism of action. This is because butyrylcholinesterase activity is most prominent in the thalamus, the projection pathways from which to the frontal lobes provide executive functions, attention, and behavioral responses, as well as in the white matter of the cerebral hemispheres. Executive function deficits are clinically manifested by impaired ability to set goals (goals), impaired ability to plan actions (ability to build a goal achievement program, identify and structure a series of steps and steps needed to achieve the goal), impaired performance of purposeful actions (difficulty starting an action and performing it, difficulty switching from one action to another), difficulties in "effective performance" (impaired ability to control and regulate one's own behavioral responses). It is possible that one reason rivastigmine is effective in Parkinson's disease-related dementia, as well as in some types of vascular dementia, is that it selectively affects the frontal areas of the brain.

The efficacy of rivastigmine in the treatment of dementia in Parkinson's disease has been convincingly proven in the large EXPRESS study, which found a positive effect of rivastigmine on cognitive function (particularly attention), activities of daily living and behavioral disorders. At present, rivastigmine is the only officially registered cholinesterase inhibitor indicated for Parkinson's disease. Rivastigmine reduces the incidence of visual hallucinations in dementia patients with Parkinson's disease. A statistically significant improvement in attention after 6 months of therapy was observed in these patients . In a multicenter double- blind placebo-controlled study that included patients with dementia with Levi's corpuscles, improvement in cognitive and emotional spheres was noted during rivastigmine therapy. The treatment reduced the occurrence of the severe psychotic disorders that are typical of this disease. It should be noted that the cognitive deficits in this disease are similar to those in AD. In addition, most patients with diffuse Levi's disease have extrapyramidal disorders (often in the absence of resting tremor), severe psychiatric disorders (including depression and psychosis) and fluctuating disorders of consciousness.

The findings are of considerable practical importance, as neuroleptics are problematic for both dementia with Levi's corpuscles and for psychotic events in patients with dementia in Parkinson's disease. In Parkinson's disease, they can exacerbate the main manifestations of the disease, and in some cases lead to the onset of a malignant neuroleptic syndrome, and in dementia with Lewy bodies, they are contraindicated.

Conclusion: Thus, current evidence suggests the importance of correcting the central acetyl cholinergic defect in patients with dementia, both in AD and due to other causes (cerebrovascular insufficiency, Parkinson's disease, dementia with Levi corpuscles, etc.). One of the drugs that perform such a correction is rivastigmine (Exelon), which inhibits acetylcholinesterase and butyrylcholinesterase. The drug has now been shown to act not only sympathetically to improve cognitive and behavioral functions in patients with AD, but also to influence the mechanisms of the disease. In addition to the tablet form of rivastigmine, a more user-friendly new form, a transdermal therapeutic system (patch), has been developed.

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