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МЕДИЧНІ НАУКИ ТА ГРОМАДСЬКЕ ЗДОРОВ'Я

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MECHANISMS OF ACTION OF DIFFERENT GROUPS OF DRUGS IN MENIERE'S DISEASE

Introduction

Meniere's disease is a chronic condition characterized by a tetrad of episodic vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural fullness [1]. The disease may also present with other audiovestibular symptoms. The prevalence of Meniere's disease is 200-500 per 100,000, which means that the disease leads to a decrease in the social activity and work capacity of a significant number of patients [2].

Symptom reduction is a challenging task in Meniere's disease. Dizziness in Meniere's disease plays a large role in reducing the quality of life of patients, and it is also a symptom that is difficult to manage. Dizziness is also a symptom with which patients often visit primary care units in modern times[12]. In addition, the presence of the symptom of dizziness is negatively correlated with a person's mental state. For example, Meniere's disease is often comorbid with depression, and vestibular neuritis - with anxiety [13].

Next, it will be possible to review the various groups of pharmacotherapy that are widely used to treat symptoms, the mechanism of action in Meniere's disease, and the effectiveness of these groups of drugs.

Modern understanding of the etiology of Meniere's disease

More than 80 years ago a correlation was discovered between endolymphatic hydrops and Meniere's disease. However, these histological changes can be observed only postmortem [1]. Because of this and the great variability in the manifestation of the disease symptoms, the etiology and early diagnosis can be complicated.

Current reviews and articles demonstrate that Meniere's disease is a multifactorial disease [3]. The factors that lead to Meniere's disease now include structural dysfunctions, genetic predisposition, and autoimmune processes. Recent studies have examined how autoinflammatory processes and vestibular migraine may be associated with Meniere's disease. Nowadays, further research on reliable endolymphatic hydrops biomarkers and real-time imaging is needed to improve the understanding and treatment of this disease [4].

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Dizziness is one of the most common reasons for primary care. According to statistical data, 2.61% of patients over 25 years old consult a doctor for dizziness. And among patients over 85 years of age about 7% of patients complain of this symptom. Also more often with dizziness apply women than men (66.7% of patients with dizziness - women). About 89.3% of patients with vertigo require medication. Common causes of dizziness are arterial hypertension, atherosclerosis, anxiety disorders, and Meniere's disease [11]. To give an example, according to the British Journal of General Practice, chest pain complaints occur at primary care in only 1.5% of cases among all age groups [12].

After the diagnosis of Meniere's disease or the syndrome is made, patients are recommended lifestyle and dietary changes in accordance with current diagnostic protocols. But for effective management of vertigo, clinicians should offer a limited course of various medications. For the prevention and effective management of acute attacks of dizziness, medications can be prescribed, which are divided into 3 pharmacologic classes: first-generation antihistamines, benzodiazepines, and anticholinergics. Chronic use of these drugs is undesirable [5].

Further, the mechanisms of action and efficacy of drugs in these groups will be presented and analyzed.

Antihistamines.

Histamine neurons are widely distributed in the central nervous system (CNS). Their nerve endings are located diffusely through the brain, including in vestibular nuclei (VN). There are four types of histaminergic receptors (HRs): H1, H2, H3 and H4. First three types are located in CNS, H4 typically found outside the CNS. H1 and H2 receptors are located at postsynaptic terminals, H3 receptors are located at presynaptic sites of histaminergic and non-histaminergic synapses. Agonists (α-methylhistamine) and antagonists (thioperamide) of H3 autoreceptors regulate the synthesis and release of histamine. Stimulation of these receptors leads to a decrease in histamine release, while their inhibition leads to an increase in histamine release. [6]

Histamine can increase the activity of VN cells directly. In vitro, histamine depolarizes rat VN neurons, which is mediated through H1 and H2 receptors. Also, the excitatory effect of histamine can be explained by a decrease in GABA levels. Histamine has been found to inhibit GABA release by acting on H3 heteroreceptors located on non-histaminergic nerve terminals, including GABAergic fibers. In general, direct and mediated activation of VN neurons by histamine results in vestibular symptoms such as: dizziness, nystagmus, and nausea [6].

Betahistine is a partial agonist of H1 receptors and an antagonist of H3 receptors. It is believed that betahistine, by binding to H1-receptors in the inner ear, promotes vasodilation and increased lymph flow, which reduces the phenomenon of dizziness [7].

Serotonine

It is known that serotonin in high concentrations can be found in the VN region. Vestibular neurons produce a large number of serotonin receptor subtypes such as 5-HT1A, 5-HT1F, 5-HT2A and 5-HT3. It is worth noting that serotonin exhibits an opposite effect to glutamate in the VN. Whereas glutamate has an excitatory effect on the vestibular nucleus, serotonin has the opposite inhibitory effect. Studies show that 5HT-1F receptors can modulate glutamate release in the VN region. Activation of these receptors leads to a decrease in glutamate release. This, in turn, may have a powerful effect in transmitting information about balance and body orientation in space. Therefore, the use of selective serotonin reuptake inhibitors (SSRIs), which increase the concentration of

serotonin in the synaptic cleft, may attenuate the excitatory effect of glutamate in VN neurons. This, in turn, would lead to an attenuation of vertigo in patients with Meniere's disease [8].

Benzodiazepines

Benzodiazepines such as diazepam and lorazepam potentiate the action of GABA in the CNS. The latter is an inhibitory neurotransmitter in the CNS, leading to repolarization of excited neurons. Thus, benzodiazepines exert an inhibitory effect in the CNS in general, and in the VN in particular. Benzodiazepines show significant efficacy in the treatment of vertigo, including Meniere's disease, when used in low doses. At these dosages, they can be used for long periods of time and will not cause dependence or drowsiness.

Some authors indicate that a single therapeutic dose of antihistamines has a more pronounced effect in the therapy of vertigo than a single therapeutic dose of benzodiazepines [9].

Nevertheless, some clinicians favor the use of low-dose benzodiazepines because at this concentration benzodiazepines effectively suppress dizziness and cause almost no side effects. At the same time, antihistamines, which pass through the GEB, cause daytime drowsiness and may be inadmissible for people with occupations requiring increased attention [10].

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