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Review
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PHARMACOTHERAPY OF VERTIGO

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Summary

Pharmacotherapy of vertigo can be symptomatic or specific. There is no ideal drug for the management of vertigo. Acute vertigo is usually managed with vestibular suppressants and antiemetic medications. Anticholinergics, antihistamines, dopaminergic antagonists, and monaminergics are most often used in the treatment of vertigo and associated symptoms. Some other drugs are also used in its treatment. However, vertigo is a subjective feeling which makes it difficult to measure the drug effect. Therefore, many papers dealing with vertigo treatment suffer from methodological pitfalls, making it difficult to establish a generally acceptable consensus about the treatment of vertigo.

Key words: vertigo, therapy, pharmacotherapy

INTRODUCTION

Vertigo is primarily due to an imbalance between the two vestibular labyrinths whose activity is modulated by the central vestibular system.

Treatment of acute vertigo has two components: to control the acute episode, and to speed up the recovery and prevent future episodes.

There is no ideal drug for the treatment of vertigo. Most of the existing drugs have essentially been found during clinical use rather than developed specifically for the treatment of vertigo. The treatment of vertigo can be symptomatic or specific. The symptomatic treatment involves controlling the acute symptoms and autonomic complaints,

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while the specific treatment should target the underlying cause of vertigo. However, some types of vertigo have a recognized pathophysiology, while pathophysiology of other types is still unknown.

In the vestibular nuclei cholinergic and H1 histaminergic receptors are the main receptor types. Sensory information from the vestibular, visual and proprioceptive systems is processed, integrated and stored. A mismatch of the sensory input produces vertigo. It seems that the cholinergic system is responsible for neural storage, the histaminergic system for stimulating the vomiting center, the GABA-ergic system inhibits signals from the cerebellar Purkinje cells, while the noradrenergic system projecting from the brainstem to the vestibular nuclei inhibits vestibular activity. Stimuli from the gastrointestinal tract are transmitted to the vomiting center through the serotonergic pathway. The chemoreceptor trigger zone in the area postrema acts on the vomiting center and can be blocked by D2 dopamine agonists, while the vestibular nuclei act on the vomiting center through the H1 histaminergic system [1-4].

Pharmacotherapy of vertigo

Many articles on vertigo treatment have been published. Searching the Pub Med on February 28, 2007 with the key words pharmacotherapy and vertigo revealed 1719 articles. However, there are few well designed, placebo-controlled, double-blind, randomized clinical trials.

Vertigo is a subjective feeling which makes it difficult to measure the drug effect. Most often more or less subjective scales are used to measure the drug effect. On the other hand, mechanisms of central compensation make most types of vertigo diminish with time. In patients with Ménière's disease Ruckenstein et al. found a remission in 60-80% of patients regardless of therapy [5]. Silverstein et al. found a remission in 59% of patients after two years and in 70% of patients after 8 years in non treated groups of patients with Ménière's disease [6]. In benign paroxysmal positional vertigo (BPPV) a remission was found in 98% patients after 3-14 days [7], and in 84% patients after one and in 93% patients after two procedures [8].

Medications are most useful for treating acute vertigo that lasts a few hours to several days. Vertigo lasting more than a few days is suggestive of a permanent vestibular injury, and medications should be stopped to allow the brain to adapt to a new vestibular input. A wide variety of medications are used to treat vertigo and the frequently concurrent nausea and vomiting.

Acute vertigo is usually managed with vestibular suppressants and antiemetic medications. Vestibular suppressants should be used for a few days at most because they delay the brain's natural compensatory mechanism for peripheral vertigo.



Four general classes of drugs are mostly used in the treatment of vertigo and its associated symptoms - anticholinergics, antihistamines, dopaminergic antagonists, and monaminergics. However, some other drugs can also be used for vertigo therapy.

Anticholinergics

It seems that the most effective drug for the prophylaxis and treatment of motion sickness is anticholinergic scopolamine. In a non-randomized study 37 patients with Ménière's disease for four weeks received anticholinergic glycopyrrolate 2x2 mg compared with placebo [9]. Glycopyrrolate significantly decreased the severity of vertigo and improved the quality of life [10].

The side effects include dry mouth, drowsiness, midriasis and accommodation disorders causing blurred vision, addiction and dependency. Anticholinergics are contraindicated in patients with a glaucoma. Newer data show that the anticholinergics selective for M2 subtypes of muscarinic receptors in the vestibular system could have fewer side effects [11].

Antihistamines

Antihistamines include *meclizine*, dimenhydrinate, and promethazine. They usually last for 4-6 hours, except for meclizine which is supposed to remain in the system for 24 hours. They generally have fewer side effects than the anticholinergics, with a sedation and drowsiness being the most prominent. However, some of these agents have some anticholinergic activity, therefore, their antivertigo action could be due to the anticholinergic activity. Such antihistamines have similar side effects as the anticholinergics [12]. The newer, nonsedating antihistamines do not enter the central nervous system and have no value in the treatment of vertigo and motion sickness.

Betahistine is an H1 receptor agonist and H3 receptor antagonist. H1 agonism causes a vasodilatation, while H3 autoreceptor antagonism increases the histamine secretion facilitating the histaminergic neurotransmission, and H3 heteroreceptor antagonism increases the secretion of other neurotransmitters improving the coordination of neuronal electrical activity in the vestibular nuclei [13].

In a double-blind, placebo controlled, crossover study 114 patients with paroxysmal vertigo were randomized to betahistine 46 mg daily versus placebo during 10 weeks. In 82 patients that finished the study betahistine decreased the frequency and intensity of vertigo [14]. In another study 81 patients with Ménière's disease were randomized to either betahistine 2x8mg daily or placebo during 3 months. Betahistine also decreased the frequency and intensity of vertigo [15]. Another study showed that in 30 vertigo patients receiving betahistine 48 mg daily during 6 weeks the frequency of vertigo diminished 61.66% after 7 days, 95.29% after three weeks, and completely vanished after



five weeks. In the same study the duration of vertigo was reduced by 53.18% after one week, and by 93.88% after three weeks [16]. However, those studies have some pitfalls. Therefore, the Cochrane Database analysis of a betahistine therapy in Ménière's disease, after analyzing the data from 6 studies including 162 patients that fulfilled the analysis inclusion criteria, concluded that there is insufficient evidence to prove that betahistine has any effect on Ménière's disease [17].

Dopaminergic antagonists

Dopaminergic antagonists such as *prochlorperazine* and *chlorpromazine* act at the chemoreceptor trigger zone, reducing the neural impulses to the vomiting center. These drugs do not prevent vertigo and motion sickness, but may be useful in treating the accompanying nausea and vomiting. *Metoclopramide* and *thiethylperazine* are mainly used as antiemetics, and in vertigo treatment they are mostly used to control the vomiting. *Metoclopramide* is a dopaminergic antagonist as well as a serotonergic antagonist which speeds gastric emptying and has a central antiemetic effect, while *thiethylperazine* acts mainly centrally on the chemoreceptor trigger zone in the medulla oblongata. The side effects of these drugs include sedation, dry mouth and extrapyramidal symptoms [18]. Newer antiemetics are serotonin 5-HT₃ receptor antagonists, like *ondansetron*, *tropisetron* and *granisetron*, they inhibit the afferent vagal impulses and the vomiting center in the medulla oblongata and are well established in patients with nausea and vomiting associated with cancer chemotherapy, radiotherapy or anesthesia and surgery. They are expensive drugs and are only seldom used in vertigo treatment [19].

Another dopaminergic antagonist, *sulpiride*, has antipsychotic, antidepressive, and antiemetic effects and could be used in vertigo treatment. *Zanetti et al.* found that 87 patients with peripheral vertigo treated with *sulpiride* for 10 days had a faster recovery than 56 patients treated with either *metoclopramide*, *thiethylperazine*, or *diazepam* [20].

Monoaminergic drugs

Monoaminergic drugs in vertigo treatment most often include *amphetamines* and *ephedrine*. They appear to potentiate the effects of *scopolamine* and may be used in combination with one of the antihistamines for intense symptoms or in those who do not respond adequately to a single-drug therapy [21,22].

Benzodiazepines

Benzodiazepines act as a vestibular suppressant through the GABAergic system. *Gamma-aminobutyric acid (GABA)* is an inhibitory neurotransmitter in the vestibular system. Benzodiazepines enhance the action of GABA in the central nervous system



(CNS) and are effective in relieving vertigo. Benzodiazepines can also minimize the associated anxiety and panic disorders that occur with vertigo. Most often prescribed benzodiazepines are diazepam, lorazepam, clonazepam and alprazolam [23,24].

Calcium channel blockers

Calcium channel blockers cinnarizine and flunarizine are possible vestibular suppressants. However, they also have anticholinergic, antihistaminic and dopaminergic effects [25]. Cirek et al. compared the effect of betahistine 3x12 mg daily and cinnarizine 20 mg plus dimenhydrinate 40 mg 3x daily during four weeks. The combination of cinnarizine and dimenhydrinate reduced vertigo intensity two times more than betahistine and reduced the intensity of accompanying symptoms. In this study no significant side-effects were recorded [26]. Another calcium channel blocker, nimodipine, was shown to be effective in Ménière's disease [27].

Other drugs

Extracts of ginkgo biloba reduce blood viscosity, improve microcirculation and are antioxidants. They increase the speed of the central compensation of vertigo in experimental animals [28], and a study showed that extracts of ginkgo biloba have similar efficiency as betahistine in the treatment of vertigo [29].

Piracetam is a nootropic agent that is a cyclic derivative of GABA. Nootropics are supposed to facilitate learning and protect the brain from physical and chemical damage [30]. Piracetam alleviates vertigo after a head injury or vertigo of central origin, as, for example, in vertebrobasilar insufficiency and in peripheral vestibular disorders, especially in middle-aged and elderly subjects. Piracetam decreases the frequency, but probably not the severity of exacerbations in patients with a chronic or recurrent vertigo [31].

Trimetazidine is an antianginal drug acting by elective inhibition of the enzyme of fatty acid β -oxidation, the long-chain 3-ketoacyl CoA thiolase (3-KAT), optimizing the myocardial metabolism in ischemia [32]. However, it has been shown that this drug could be effective in vertigo treatment. In 20 patients with Ménière's disease trimetazidine 3x20mg daily compared with betahistine 3x8mg daily during 3 months decreased vertigo frequency and intensity, while there was no difference in the hearing, tinnitus, sensation of ear fullness and quality of life [33]. Another study on 45 patients with Ménière's disease showed that trimetazidine 3x20mg daily compared with betahistine 3x12mg daily during 2 months had beneficial effects on vertigo intensity, while there was no difference in the hearing and tinnitus [34].

Some antiepileptics are also efficient in vertigo therapy, like phenonon which is effective in motion sickness [35], as well as gabapentine, carbamazepine and oxcarbazepine [24]. Gabapentine suppresses nystagmus possibly through GABAergic action [36].



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Sažetak

Farmakoterapija vertiga

Farmakoterapija vertiga može biti simptomatska ili specifična. Ne postoji idealni lijek za liječenje vertiga. Akutni vertigo se obično liječi vestibularnim supresorima i antiemeticima. U liječenju vertiga i pridruženih simptoma najčešće se primjenjuju antikolinergici, antihistaminici, dopaminergički antagonisti i monaminergici. I neki drugi lijekovi se također primjenjuju u liječenju vertiga. Međutim, vertigo je subjektivni osjećaj, što otežava mjerenje učinka lijekova. Stoga mnogi radovi o liječenju vertiga imaju metodološke poteškoće, što otežava donošenje opće prihvaćenog konsenzusa o liječenju vertiga.

Ključne riječi: vertigo, terapija, farmakoterapija