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Current Perspectives In The Pharmacotherapy Of Vertigo

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ABSTRACT

Vertigo is a symptom encountered very commonly in clinical practice due to a disorder in the vestibular system. In addition to dizziness it is very often accompanied by nausea and vomiting. Pharmacotherapy plays an important role in the management of vertigo. Vestibular suppressants and drugs to control nausea and vomiting constitute the mainstay of the pharmacotherapy of vertigo. Specific drug therapy can be given in patients where the underlying disease process causing the vertigo has been identified. Despite the availability of many classes of drugs, there are no definitive, universally accepted guidelines for the treatment of vertigo which makes it even more difficult to follow first-, second- and third-line therapies when treating patients. It is difficult to establish guidelines or a generally acceptable consensus in the treatment of vertigo due to the complexity of vertigo and lack of adequate randomized clinical studies.

Keywords: Vertigo, Pharmacotherapy, Vestibular suppressants Pharmacotherapy, Vertigo, Cinnarizine, Beta-histine, Dizziness.

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INTRODUCTION

The enigma and difficulty in the treatment for vertigo is due to the fact that it is not a definite disease but a symptom. Vertigo usually occurs due to a disturbance in the vestibular system.

Depending on their etiology though, vestibular diseases can be treated with drugs, physical therapy, psycho-therapeutic measures and rarely surgery. Pharmacotherapy plays a crucial role in the management of vertigo. Till date it has been only possible to treat vertigo as a symptom and not a disease. Understanding pathophysiology plays an important role since it helps in deciding appropriate pharmacotherapy.

The vestibular system includes end organs which are the bony labyrinths of the inner ear consisting of three semicircular canals, the utricle and saccule (otolithic apparatus) on each side. The angular and the linear acceleration produced in the semicircular canals and otolithic apparatus gives an individual a sense of head position in space. The neural output of these end organs is conveyed to the vestibular nucleus in the brain stem via the eight cranial nerve.[1]

The neural projections further to the III, IV and VI cranial nerves as well as spinal cord, cerebral cortex and cerebellum provide conscious awareness of head position and movement.[1]

The vestibular system is one of the three sensory components helping an individual to attain spatial orientation and posture; whereas the other two being the visual and somatosensory systems.

The neurotransmitters required to be manipulated are the ones involved in vestibular transmission namely which are released in the cholinergic, monoaminergic and glutamatergic synapses and involved in central and peripheral vestibular circuits. There are several neuro-transmitters which influence the 'three neuron arc' between the vestibular hair cells and oculomotor nuclei that drives the vestibulocular reflex.[2]

Glutamate is the major excitatory neurotransmitter acting through the N-methyl-D-aspartate (NMDA) receptors in the

vestibular nerve fibers.[3-5] M2 cholinergic receptors are involved with dizziness.[6] Gamma-aminobutyric acid (GABA) an inhibitory neurotransmitter is found in the vestibular neurons leading to stimulation of GABA-A and GABA-B receptors.[7] Histamine acts on H1 and H2 receptors present pre- and postsynaptically on vestibular cells and affects vestibular response. Dopamine and noradrenaline also modulate the intensity of reactions to the vestibular system.[8,9] Adrenocorticotropic hormone (ACTH) has been reported to accelerate vestibular compensation.[10]

This below article focuses exclusively on the pharmacotherapy of vertigo which is due to a disturbance in the vestibular system; excluding the other causes like motion sickness and orthostatic hypotension.

Pharmacotherapy of Vertigo

There is a paucity of information on the drug treatment of vertigo even today, since there have been no multicentric, well controlled clinical studies to demonstrate the advantage of treatment over no treatment.[11]

In patients suffering from migraine, epilepsy or Meniere's disease where the cause of the vertigo is known specific drug treatment is possible. But this scenario is very rare keeping in mind the number of patients suffering from vertigo.

Vestibular suppressants are the mainstay of treatment in patients suffering from vertigo today. These drugs reduce the asymmetry in the vestibular tone between the ears and thereby reduce vertigo.[1] They include anticholinergics, antihistaminics, antidopaminergic drugs and benzo-diazepines.

Anticholinergics: They act on muscarinic receptors and increase motion tolerance. Only centrally acting anticho-linergics are useful in treating vertigo. Scopalamine is one of the most effective singly acting agent to prevent vertigo by acting on the M3 and M5 receptors.[8] These drugs have prominent side effects like dry mouth, dilated pupils, sedation, decreased alertness and impaired attention. Prolonged use of scopolamine as a transdermal patch may also lead to chemical addiction.[12] Anticholinergics selective for vestibular subtypes of muscarinic receptors are being developed, one such being zamifenacin.[13,14]

Antihistaminics: The H1 blockers are currently the most commonly prescribed drugs for vertigo which include; diphenhydramine, cyclizine, dimenhydrinate, meclizine and promethazine.[15,16] This is the only class of drugs being quoted as having antivertigo properties.[17] Meclizine is the only long-acting drug among the antihistaminics used. They have lesser side effects in comparision with anticholinergics. Some antihistaminics have side effects similar to anticholinergics, since the antivertigo effect is due to their anticholinergic property.[8]

Cinnarizine: It plays an important role in the treatment of vertigo by blocking the entry of calcium into the plasma-membranes especially after adrenergic stimulation.[18] The basic action of this drug is acting as a labrynthine sedative.[19]

Histaminergic medications: This class of drugs is represented by betahistine which is an analogue of L-histidine, the immediate precursor of histamine. The antivertigo effects of betahistine are sometimes explained as a vasodilatory effect, improving blood flow in the microcirculation of the internal auditory and vestibular systems.[20,21] It has a complex effect on histamine receptors, being both a partial H1 postsynaptic agonist causing vasodilation and H3 presynaptic antagonist increasing histamine secretion, leading to final facilitation of histaminergic neurotransmission.[22,23] This improves neuronal electrical activity in the vestibular nuclei.[24]

Dopaminergic antagonists: These drugs are commonly used to control nausea in vertiginous patients. Several antipsychotics namely phenothiazine derivatives and butyrophenones are popular in this condition.[25] Neuroleptics exert an antiemetic effect by blocking the dopaminergic receptors in the area postrema of the brain stem. They reduce the neurovegetative symptoms that commonly parallel vertigo and may improve the psychoaffective symptoms accompanying vertigo. These drugs are not known to exert specific dopaminergic vestibular effects but do possess anticholinergic and antihistaminic (H1) properties that explains a vestibular suppressant activity.[2]

Drugs like metoclopramide which is a dopaminergic antagonist as well as serotenergic antagonist speeds up gatric emptying and has a central antiemetic effect by acting on the chemoreceptor trigger zone in the medulla oblongata. The side effects of these drugs are sedation, dry mouth and extrapyramidal symptoms.

The newer 5HT3 antagonists like ondansetron, tropisetron and granisetron inhibit the afferent vagal impulses and the vomiting center in the medulla oblongata are used as drugs of choice in cancer chemotherapy, radiotherapy and surgery or anesthesia induced vomiting. These drugs seldom play a role in controlling nausea and vomiting in vertigo.[26]

Some H1 antihistaminics like promethazine also block dopamine receptors, and hence, useful in vertigo.[14]

Benzodiazepines (BZDs): They act as vestibular suppressants through the GABA ergic system. GABA is an inhibitory neurotransmitter of the vertibular system. BZDs enhance the role of GABA in the central nervous system and effective in relieving vertigo and associated anxiety and panic disorders.[27,28] They also cause muscle relaxation, anterograde amnesia and have muscle relaxant property.

The most often prescribed BZDs are diazepam, lorazepam, clonazepam and alprazolam.[27,28]

Calcium antagonists: Cinnarizine which features as a antihistaminic above and flunarizine have been used as antivertigo drugs.[29,30] Both these drugs prevent motion sickness and are vestibular depressants since the vestibular hair cells have calcium channels.[31,32] It is postulated that calcium channel blockers inhibit the flow of calcium from

the endolymph to the cells of the crista ampullaris which is required for trigerring an action potential that is propagated centrally.[33] They also have anticholinergic, antihistaminergic and antidopaminergic actions.[34]

Another calcium channel blocker nimodipine was shown to be effective in Meniere's disease.[35]

Anticonvulsants: Gabapentin, carbamazepine and oxcarbazepine are used in the treatment of vertigo although not studied extensively. They are preferred for the treatment of nystagmus.[36] Another GABA agonist, baclofen has been tried for vertigo by reducing vestibular asymmetry; though no human trials have been undertaken.[37]

Sympathomimetics: Sympathomimetic drugs enhance vigilance and counterbalance the sedative effects of other antivertigo drugs like antihistaminics.[14] The addictive potential of amphetamines makes the use of these drugs rare.

Table 1: List of drugs used in vertigo[13,42-50]

Class/drug (s)	*Action*	*Drug*	*Dosage*
Vestibular suppressants			
Antihistaminics	H1 blockade; they inhibit activation of central cholinergic pathways by suppressing vestibular end-organ receptors. Also possess additional anticholinergic and sedative action	Diphenhydramine Dimenhydrinate Meclizine Cyclizine Promethazine Cinnarizine Flunarizine* Astemizole	25-50-100 mg 6 hrly 50 mg 4 to 6 hrly 25-50 mg daily 25-50 mg 6 hrly 25 mg 12 hrly 25 mg 4-6 hrly 10 mg daily 10 mg 8 hrly
Anticholinergics	M1, M2, M3 blockade; inhibit activation of central cholinergic pathways	Atropine sulfate hyoscine (scopolamine) Zamifenacin	0.4 mg IM PO. 0.6 mg 3 to 4 hrly Transdermal patch of 1.5 mg delivering 1 mg 3 hrly
Phenothiazines	Act by suppressing central vestibular nuclei and pathways	Prochlorperazine, thiethylperazine	10 mg 4 hrly 6.5 mg 8 to 24 hrly
Psychotherapeutic agents			
Benzodiazepines	Act on GABA A site on vestibular nucleus; helpful in vertigo since modify sensation of vertigo	Diazepam Lorazepam Clonazepam	PO-2, 5, 10 mg BD-QID slow IV 5-10 mg 4 hrly 1 mg 8 hrly 0.5 mg 8 hrly
Antidepressants	Tricyclic antidepressants	Amitriptyline Nortriptyline	25 mg 8 hrly 10 mg 8 hrly
Vasodilators	Improve blood flow to labyrinth and brain stem and act on histamine agonists	Betahistine	32-72 mg daily
Diuretics	Decrease intralabyrinthine fluid pressure	Acetazolamide Hydrochlorothiazide	250 mg daily for 2 out of 3 days 25 mg 12 hrly
Miscellaneous			
Anticonvulsants	Stabilization of neuronal membranes in CNS	Phenytoin	–
Nootropic agents	Modify sensation of vertigo	Piracetam Ginkgo biloba	400-800 mg 8 hrly
Dopaminergic agonists	Alleviates symptoms	Piribedil, bromocriptine	–
Antiemetics	Dopaminergic antagonists	Metoclopramide	10 mg PO TID or 10 mg IM
Antiemetics	5-HT_3 antagonists	Ondansetron Granisetron Tropisetron	4-8 mg PO TID 32 mg IV one dose 1 mg PO BID 10 ug/kg IV daily
GABA agonists		Baclofen	5 mg TID
Acetyl-leucine	Anticalcium properties	Acetyl-leucine	500 mg 8 hrly

Neuroleptic	Antiadrenergic and antidopaminergic	Droperidol/fentanyl	IM/slow IV: Droperidol 2.5-5 mg/fentanyl 50 μg/ml 12 hrly
Other new agents under trials	NK1 receptor blockade NMDA blockade	GR203040 LY233053 ORG2766	–

* Also acts as calcium antagonist. Other calcium antagonists like nimodipine are also found to be useful

Miscellaneous agents: Apart from the drugs mentioned above, there are many other drugs which have shown beneficial effects in the treatment of vertigo. However, it is interesting to note that many drugs have not yet been approved by regulators in many countries since they lack randomized clinical studies proving their efficacy against vertigo. Evidence available for these drugs comes from anecdotal data, case reports, review articles or clinical studies conducted with little number of patients.

Acetylleucine was aggressively marketed in France for vertigo.[38-40] It may act as a precursor of a peptidic neuro-mediator responsible for activation of vestibular afferents. It may also have 'anticalcium' properties on neurotrans-mission. Oral and intravenous formulations are available.

Piribedil is an dopaminergic agonist used as an antivertigo agent.[41] Vertigo is an example where both agonists and antagonists have shown to produce sympto-matic relief owing to the complexity of the condition.

Piracetam is a nootropic drug that is a cyclic derivativeof GABA. It alleviates vertigo after a head injury or vertigoof central origin, especially in vertebrobasilar insufficiency.It only decreses the frequency and not the severity ofexacerbations in patients with chronic or recurrent vertigo.[42]Ginko biloba causes increase in microcirculation and also possess antioxidant properties. Some studies haveshowed an equal efficacy of ginko biloba and betahistine in the treatment of vertigo.[43]

Bromocriptine may speed vestibular compensation and hence tried as an antivertigo drug.[44]

Trimetazidine, which is a selective inhibitor of 3 ketoacyl CoA thiolase enzyme used in angina has been tried for vertigo.[45-47]

Droperidol and fentanyl : Though it has no beneficial effect in chronic vertigo, a combination of droperidol and fentanyl has been tried for acute peripheral vertigo.[48]

Diuretics: Hydrochlorothiazide has been known to improve vertigo due to Meniere's disease by decreasing the intralabyrinthine fluid pressure.[49,50]

Despite presence of the drugs mentioned above and summarized in the table (Table 1), there are still lot of questioned which need to be answered. Drug dosage, duration, combination therapy, drug interactions, use of drugs as primary agents and in refractory cases are some of these questions which need to be scientifically answered by designing well-planned clinical studies.

CONCLUSION

There is a high incidence of patients presenting to the otorhinolaryngology clinics with vertigo. Depending on whether the patient is suffering from acute vertigo or chronic vertigo, the clinician has to use his expertise to select specific drugs for optimum patient benefit. It needs to be stressed that the cure for vertigo is not permanent, unless the underlying disease process is identified. Thus, the duration of therapy for vertigo can only last for a few days. This article outlines many targets and drugs available for the treatment in vertigo. However, it is important to note that many drugs do not have adequately powered, randomized clinical studies proving their efficacy in vertigo and many drugs are not approved for the use in vertigo. This definitely highlights the need to have well-defined clinical studies and newer drugs which would address unanswered questions and unmet needs experienced in the treatment of vertigo.

PHARMACOTHERAPY IN VERTIGO

Vestibular sedatives or vestibular suppressants are the mainstay of treatment for patients with vertigo. These drugs help to reduce the asymmetry of the vestibulartones between the two labyrinths and so reduce the vertigo.[11] Common antivertigo drugs include anticholinergic, antihistaminic, antidopaminergic and benzodiazepines. Frequently used antivertigo drugs are given in (Table 2).

Anticholinergics :

These drugs act on the muscarinic receptors and increase motion tolerance. The anticholinergics those are acting centrally, useful for treatment of the vertigo. Scopolamine is a highly effective agent used to prevent the vertigo by acting on the M3 and M5 receptors.[12] Anticholinergics have side effects like dilated pupils, dry mouth, decreased alertness, sedation and impaired attention. Long term use of scopolamine as a trans-dermal patch can lead addiction. The selective anticholinergic for acting on vestibular specific muscarinic receptors are developed, one such is zamifenacin.[13]

Antihistamines

The H1 receptor blockers are often prescribed medications for vertigo. These antihistamines include cyclizine, diphenhydramine, dimenhydrinate, meclizine and promethazine.[14]

Meclizine is considered as a long acting drug prescribed among all antihistamines. These drugs have lesser side effects than anticholinergic drugs. Few antihistamines have side effects and these side effects are similar to anticholinergics, as the anti-vertigo effect is usually by their anticholinergic properties.[12]

Meclizine is effectively controlling symptoms of the motion sickness like nausea, vomiting and vertigo. It has also anticholinergic effect. It suppresses the labyrinthine stimulation. The recommended dose of the meclizine is 25 to 50 mg orally, taken one hour before the travel. This drug may be repeated every 24 hours as per requirement.

Cyclizine is a piperazine derivative and has anti-motion sickness effect like dimenhydrinate. It has less sedative effect.[15]

Table 1: Frequently used anti-vertigo drugs in clinical practice.

Drugs	Mechanism of action	Dose	Used in	Side effects
Cinnarizine	Selective calcium channel blocker and it acts primarily on the peripheral vestibular labyrinth by interfering local calcium ion flux	75 mg per day	Peripheral causes of vertigo	Sedation, weight gain, pedal edema, extrapyramidal disorders
Cinnarizine and dimenhydrinate	Cinnarizine is calcium channel blocker. Dimenhydrinate regulates vestibular nuclei and adjacent vegetative nuclei and adjacent vegetative centers in the brainstem. Dimenhydrinate enhances the actions of cinnarizine	Cinnarizine 20 mg and Dimenhydrinate 40 mg/day	Vertigo and motion sickness	Affect the occupation and cognition extrapyramidal side effects, high somnolence
Prochlorperazine	A potent neuroleptic, it acts as D2 blocker in chemoreceptor trigger zone (CTZ) and has anticholinergic effects also	10-15 mg per day	Acute vertigo	Drowsiness, dizziness and dry mouth
Beta-histine	It is a histamine analogue which stimulates H1 and H2 receptors in vestibular nuclei and brain stem	48 mg per day	Vertigo	Mild side effects like gastrointestinal complaints, fatigue and altered taste
Diazepam	Causes inhibition throughout the central nervous system, including activity in the vestibular nerve and vestibular nuclei	5 mg/6-8 hours	Anxiety and vertigo	Drowsiness, dizziness and respiratory depression

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