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An update on pharmacotherapy of vertigo

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ABSTRACT

Vertigo is a specific symptom directly related to dysfunction of vestibular system. It is most common complaint, especially in elderly age group that leads them to visit their physicians. There is no ideal drug for the management of vertigo. The pharmacotherapy of vertigo can be optimized with detailed knowledge of the drugs effective in vertigo and their limitations. In this article, we will discuss the pharmacological options that are available for the treatment of vertigo along with some recent advances.

Key words: Vertigo, pharmacotherapy, antivertigo.

INTRODUCTION

Vertigo is a sensation of movement when no movement is actually occurring. Three senses are used to convey streams of sensation: visual, vestibular, and somatosensory. When there is a mismatch between information carried on two or more senses, vertigo is perceived. Vertigo is primarily due to an imbalance between the two vestibular labyrinths whose activity is modulated by the central vestibular system. There are several transmitters in the vestibular nuclei but cholinergic and H1 histaminergic receptors are the main types. Beside these monoaminergic, glutaminergic, gamma-aminobutyric acid, serotonin and neurokinin type 1 receptors have been demonstrated in vestibular afferent. Four general classes of drugs are useful in the treatment of vertigo and its associated autonomic symptoms - anticholinergics, antihistamines, antidopaminergics and monaminergics. Refinement of medications to target these synapses exist

for the future so that specific antagonists to muscarinic and histamine receptors can eventually be made without the adverse effects of broadly acting antagonists. Besides this many newer drugs are being tried for the treatment of vertigo. Therapy of vertigo is optimized when the prescriber has detailed knowledge of the pharmacology of medications being administered as well as the precise actions being sought. In this article, we will discuss the pharmacological agents that are available for the treatment of vertigo and various other drugs still under investigation. Broadly we can divide the agents used for the treatment of vertigo as vestibular suppressant, antiemetics and agents with non specific mechanism of action.

Vestibular Suppressant

Vestibular suppressants, generally speaking, are drugs that reduce nystagmus caused by a vestibular imbalance, or drugs that reduce motion sickness. Table 1 lists commonly used vestibular suppressants.[1] These drugs fall into three major groups: benzodiazepines, anticholinergics and antihistamines.

Table 1. Selected medications approved for vertigo

Drug	AV*	CV	Site of action	Dosage	Adverse effect
Benzodiazepams	+	+	GABA A on vestibular nucleus		Sedation, addiction
Diazepam				PO-2,5,10mg bd-qid Slow IV-5-10mg q4h	
Lorezepam				PO- 1-2 mg tds	
Clonezepam				PO- 0.5 mg tds	
Antihistamines		+	H1 blockade, Anticholinergic		Sedation
Diphenhydramine				PO-25-50 mg q4h-q6h IV/IM-10-50mg qid	
Dimenhydramine				PO- 50 mg q4h-q6h IV/IM-25-50mgq4h-q6h	
Meclizine				PO- 25-50 mg qd-qid	
Cyclizine				PO- 50 mg q4h-q6h	
Promethazine				PO- 25 mg q6h IM-25mg q4h-q6h	
Anticholinergics					
Scopolamine		+	M_1, M_2, M_3 blockade (M_3 most important)	PO- 0.6 mg q4h Transdermal 1.5 mg Patch delivers 1 mg q3h	Sedation dry mouth acute angle laucoma, dermatiits
Neuroleptics					
Droperidol/Fentanyl	+		Antiadrenergic and Antidopaminergic effects	IM/slow IV: Droperidol 2.5-5mg/Fentanyl 50 µg/ml q12h	Hypotension, Respiratory depression

**AV- Acute vertigo; # CV- Chronic vertigo*

Benzodiazepines

They act centrally via GABA-A receptors to suppress vestibular responses. Lorazepam is a particularly useful agent because of its effectiveness and simple kinetics. Low doses of diazepam (2mg) can also be quite effective. Clonazepam, which has marked antiepileptic properties, has

reported to control vertigo as effectively as lorazepam.[2] Addiction, sedation, impaired memory, increased risk of falling and impaired vestibular compensation are their main shortcomings. Addiction can usually be avoided by keeping the dose less. Long acting benzodiazepines are not helpful for relief of vertigo.

Anticholinergics

Anticholinergic medications act on muscarinic receptors and increase motion tolerance. Only centrally acting anticholinergics are useful in treating vertigo.[3] Pure anticholinergics are ineffective if administered after symptoms have already appeared. Scopolamine is one of the most effective single agent in preventing vertigo. Anticholinergics have prominent side effects of dry mouth, dilated pupils, sedation, decreased alertness and impaired attention. Addiction and psychosis have also been reported with more than one-month use of scopolamine.[4] Studies have indicated that M_3 and M_5 receptors may be responsible for the beneficial effect of anticholinergics. Agents selective for vestibular subtypes of muscarinic receptors are being developed as these agents may provide vestibular suppression with fewer side effects. Zamifenacin is a new selective M_3 and M_5 anticholinergic under investigation.

Antihistamines

The precise role of histamine in central vestibular processing is uncertain. All the antihistamines used for control of vertigo have anticholinergic activity. It has been argued that their antivertiginous property is not due to H1 effects but rather the result of their central anticholinergics actions. Promethazine is most effective among all the antihistamines. Antihistamines prevent motion sickness and reduce the severity of its symptoms, even if taken after the onset of symptoms.[3] The most frequent side effect encountered by the use of antihistamines is sedation. Some of the antihistamines like cinnarizine also have calcium channel blocking activity.[5]

Antiemetics:

The choice of antiemetic agent depends mainly on considerations of the route of administration and the side effect profile. Some antihistamines commonly used as vestibular suppressants have significant antiemetic properties (e.g. meclizine). When an oral agent is appropriate, this agent is generally the first to be used, because it rarely causes adverse effects any more severe than drowsiness. Neuroleptic droperidol, a derivative of haloperidol is used exclusively in anaesthesia for its sedative and antiemetic property. Currently combination of droperidol and fentanyl is being used for control of acute peripheral vertigo with encouraging results.[6] Phenothiazines, such as prochlorperazine and promethazine, are effective antiemetics, Because of significant side effects, such as dystonia, they are considered second-line drugs whose use should be brief and cautious. Theoretically, newer antiemetics, 5-HT_3 antagonists might not be ideal for emesis related to vestibular imbalance. A highly selective dopamine (D_2) receptor antagonist, l-sulpiride, is under investigation for anti motion sickness effects.

Agents with non specific mechanism of action:

Table 2.Selected investigational medications and agents not approved in the U.S.

Drug	Motion sickness	Vertigo	Possible mechanism of action
Anticholinergics			
Zamifenacin	+		M_3 and M_5 blockade
Anticonvulsant			
Phenytoin	+		Stabilisation of neuronal membranes in CNS
Calcium antagonists			
Flunarizine	+	+	Labyrinth suppression, possibly at the level of the vestibular hair
Cinnarizine			
Nimodipine			
Tricyclic antidepressant			
Doxepin	+		Strong H_1 antagonist, adrenergic and Anticholinergic effects, weak dopaminergic effect
Serotonergics			
8-OH-DPAT	+		$5HT_{1A}$ agonist effects probably in the vestibular nuclei Increase in concentration of serotonin in synapse
Imipramine/ Fluoxetine	+		
Others			
GR203040	+		NK_1 receptor blockade
LY233053	+		NMDA blockade in the vestibular nuclei and the Final common pathway for vomiting Suppression of vestibular nuclei
ORG2766	+		

Calcium channel blockers

Calcium channel blockers are the most promising agents in this group. It is postulated that calcium channel blockers inhibit the flow of calcium from the endolymph into the cells of the crista ampullaris, which is required for triggering an action potential that is propagated centrally.[7] However, calcium channel blockers often have anticholinergic and/or antihistaminic activity and the relative importance of calcium channel blocking activity for vestibular suppression has not been determined. Flunarizine and cinnarizine, have powerful labyrinth suppressant action and have efficacy comparable to prochloperazine. They are popular antivertiginous agents outside United States. Potential side effects of these agents include weight gain, depression and sedation. Nimodipine has recently been reported to be effective as prophylaxis of menieres in the dose of 30mg twice daily.

Anticonvulsants

Anticonvulsants are promising agents for treatment of vertigo. Phenytoin, a sodium channel blocker has also been recently reported to be protective against motion sickness.[8] Gabapentin, carbamazepine and oxcarbazepine are also sometimes successfully used in treatment of vertigo, although their use has not been studied extensively. Another GABA agonist, baclofen has shown some promise in reducing vestibular asymmetry. No human trials have yet been undertaken.

Histamine agonists:
The antihistamines used in treating vertigo are usually centrally acting histamine H1-receptor antagonists, but betahistine is an H1+H2-receptor agonist. The rationale for use of betahistine is that it is said to increase circulation to the inner ear or affect vestibular function in some mysterious way through activity of H3 receptors.[5] Pragmatically, a betahistine dose of 8mg three times/day is usually prescribed, although greater effect is obtained for doses as high as 32 mg. Betahistine is not fully approved by the FDA in the US. It is found to be moderately effective in suppressing symptoms of meniere's disease.

Antidepressants :
Some of the tricyclic antidepressants like imipramine and doxepin have been investigated for anti motion sickness. They have shown favorable results but exact role needs to be defined. Also, some antidepressants such as amitriptyline have strong anticholinergic properties, which can be of use in managing dizziness.

Steroids:
Corticosteroids such as decadron have been advocated both for treatment of meniere's disease and vestibular neuritis, in both cases, in an attempt to reduce the duration of a vertiginous episode. This use has not been studied formally.

Sympathomimetics:
The mechanism of action of amphetamine and ephedrine in preventing motion sickness is unclear. One theory attributes their antimotion sickness effects to the enhancement of selective dopaminergic stimulation. Moreover sympathomimetics may increase alertness and thereby counterbalance the sedative effects of vestibular suppressants. Amphetamines are little used because of their addiction potential.

Miscellaneous agents:
Acetyl-leucine and Ginkgo Biloba are said to act as vestibular suppressant widely marketed and largely used in France.[9] These agents are not used in the US for vertigo, as they lack clinical trial to support their use.

Future trends
Selective serotinin reuptake inhibitors are being tested in the animal models for effectiveness in motion sickness, but their role in humans is not clear.[10] Some NK_1 receptor antagonists are found to exert strong antiemetic property, but no demonstrable effect was found in motion sickness.[11] NMDA receptor antagonist has been shown to act in blocking both motion sickness and chemical induced emesis in cats.[12] Animal studies have also shown that short adrenocorticotrophic hormone (ACTH) fragments relieve vertigo symptoms and accelerate their disappearance.[13]

CONCLUSION

Presentation of patients with vestibular complaints is a common occurrence in the otolaryngology clinic. Vestibular suppressant and antiemetic drugs are the mainstay of treatment of vertigo. Pharmacotherapy of vertigo is optimized when the prescriber has detailed knowledge

of the pathophysiology of vertigo and the pharmacology of medications being administered as well as the precise actions being sought. It is also important to consider a medication's onset of action. A drug with a rapid onset of action is required to treat acute vestibular vertigo or ongoing motion sickness, whereas a slow-acting medication is appropriate for chronic vertigo.

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